BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 11 1951

THE MECHANISM OF "CONVERSION"*

BY

WILLIAM SARGANT, F.R.C.P.

Physician in Charge, Department of Psychological Medicine, St. Thomas's Hospital, London

> "We talked of preaching and of the great success that the Methodists have. He [Johnson] said that was owing to their preaching in a plain, vulgar manner, which was the only way to do good to common people. . . . He said that talking of drunkenness as a crime, because it debases reason, the noblest faculty of man, would do no service to the vulgar. But to tell them that they might have died in their drunkenness and show how dreadful that would be, would affect them much."
>
> *Boswell's London Journal*,† p. 329.

Religion, politics, and psychiatry often face a common problem—that of seeking the most effective means of bringing about rapid changes in an individual's beliefs and actions and afterwards trying to stabilize them. When I first became interested in the similarities of methods sometimes used by all three disciplines towards the end of the recent war, I little expected it to have the growing importance that attaches to it at the present time (Sargant and Shorvon, 1945). But the world suddenly finds itself again facing ideational conflicts, the outcome of which may decide its fate for centuries. The problem of the psychiatrist and his patient, of the religious leader seeking to gain and hold new converts, has now sometimes become the problem of groups of nations who not only wish to maintain certain beliefs within their boundaries but to gain fresh adherents to these beliefs from without.

Recently, for instance, Mrs. Charlotte Haldane pleaded that urgent psychological research should be undertaken into the mechanisms of the process by which she, the intelligent wife of a well-known British scientist, was converted to belief in Russian interpretations of Marxian dialectics, and, having accepted and followed these for many years, why the falsity of the whole system became apparent to her in an equally intense reconversion experience. Koestler and others have also described the same type of happening in their lives. There is also the bewilderment with which people witness the preparation of a person for his trial behind the "iron curtain" by a method which makes him not only believe but proclaim to the world that his past actions and ideas have been wrong and worthy of death, though shortly before he had thought them to be both right and honest.

These are, however, only examples of the same process occurring, for instance, in a person who, after a religious conversion, may suddenly come to believe that a life of exemplary good works has not only been useless but even accompanied by the perils of eternal damnation because acceptance of one particular religious attitude has been neglected; or one who, after being subjected to psycho-analysis, is convinced that his past behaviour has been due to an intense underlying hatred of his father though he has previously always felt and acted in a particularly devoted manner to him. How are people induced to believe what may even be the opposite of the ascertainable facts?

Though both must overlap to some extent, the gradual and minor changes of outlook and behaviour of an individual, based on increasing maturity and experience, must be distinguished from those abrupt and total reorientations of viewpoint and action, often brought about by others, which involve the giving up of cherished beliefs, the adoption of new ideas, and perhaps views diametrically opposed to those previously held.

Physiological Aspects

In this lecture I wish to discuss some of the more physiological aspects of this problem in which I became interested by a fortuitous combination of circumstances. The recent war provided one of those rare opportunities of studying the breakdown of normal persons subjected to intense stresses. Drug abreactive techniques and other physical methods of treatment proved of great importance as aids to psychotherapy in such patients, and so became the subject of intensive research (Sargant, 1948). At the same time the first English translations of Pavlov's (1941) lectures on conditioned reflexes and psychiatry had appeared. And it was found that the symptomatology exhibited, and many of the empirical treatments discovered to be useful in breaking up the abnormal mental pattern occurring in war neuroses, had, in fact, been anticipated by Pavlov in his many years of work on experimental neuroses in animals. This suggested the desirability of a more careful study of his findings in relation to psychiatry than had been afforded them in recent years in Britain.

Seen in broad perspective, some of the phenomena witnessed during the abreactive and physical treatments of war neuroses also seemed to have many basic similarities to those reported in the literature of sudden religious conversion. After the war an opportunity suddenly presented itself of seeing at first hand in the U.S.A. some of the more violent and radical religious

*A lecture given at the Faculty of Medicine in Lisbon on May 15 and at the British Institute in Madrid on June 8.

†Edited by F. A. Pottle, 1950. William Heinemann, London.

conversion methods still practised in parts of that country (Sargant, 1949). It seemed particularly important to learn more about these, as history showed that they had been able to change the face of England during the Methodist revival of the eighteenth century. As a result of the methods used then, which have largely died out in England but are preserved in the New World, it has been recorded that large numbers of the common people in England were so permeated by new religious attitudes that they became relatively impervious to the materialistic propaganda of Tom Paine and the French Revolution which swept the rest of Europe (Magnus, 1939). They had been made temporarily much more concerned about their fate in the next world than about conditions in the present one.

Physiological mechanisms are obviously only a part of the total process; but, because their importance is so often overlooked by those believing in the transcendency of reasoned argument over other methods, we are behind others in their use and understanding at the present time, and are often frankly bewildered when we see them in action and come face to face with their sometimes devastating effects on the human mind.

Experimental Findings in Animals Related to Man

In 30 years' experimental work on animals Pavlov accumulated a mass of observation on the various methods available for building up conditioned patterns of behaviour in the nervous system and breaking them down again (Frolov, 1938; Pavlov, 1941). Many physiologists and psychiatrists dispute Pavlov's mechanistic interpretations of his findings, but the actual experiments themselves have been confirmed repeatedly.

One observation of his seems especially important when considering the problem of suddenly induced changes of outlook and behaviour. A group of his dogs, conditioned after months of patient work, were trapped accidentally in their cages during the Leningrad flood of 1924. When finally rescued they were swimming about in their cages with their heads just above the still rising water. After being rescued some of them passed abruptly into a state of temporary cortical inhibition amounting to stupor, because of the fear and excitement experienced. The physiological shock had proved to be beyond the capacity of their nervous systems to deal with adequately, and had brought about what Pavlov termed "protective" cortical inhibition.

This traumatic experience had other interesting effects, for when the dogs were tested again after the inhibitory activity had passed off it was found that those who had shown this switch-over from profound excitation to severe inhibition had had many of their recently implanted conditioned reflexes dramatically abolished. Those dogs which had responded to their experience with strong excitement only were much less affected.

Great importance was attached by Pavlov to this chance observation, and it was eagerly followed up, for it seemed to provide a new and speedy means of breaking up implanted behaviour patterns in the nervous system, and in some of the dogs a completely new set of conditioned reflexes could be substituted with the abolition of the old. The weakest of the animals, however, were made permanently unstable by this experience; they were never able again to be reconditioned satisfactorily. This was termed a "physiological" rupture of higher nervous activity. Even in those in which a later satisfactory reconditioning was achieved, marked sensitization to their traumatic experience remained. Months afterwards a trickle of water underneath the door of the laboratory would still produce obvious changes in their behaviour.

These findings may be relevant not only to the mechanics of a sudden conversion process but to an understanding of parallel findings in psychiatry after the use of drug abreactive techniques, shock treatment, etc. They probably also help to explain the building up of what psycho-analysts have termed "transference" situations that arise between therapist and patient during treatment.

Types of Inhibitory Phenomena

Psychiatrists outside Russia have also paid far too little attention to Pavlov's repeated emphasis on other types of pathological activity of the cortex that occur whenever the nervous system is stimulated, either psychologically or physiologically, beyond its particular limit of tolerance. (In the human subject fear-provoking thoughts and guilt feelings can be as productive of this form of "transmarginal" stimulation as other means of bringing it about in animals.) A state of increasing and uncontrolled excitement may supervene. But more commonly the cortex finally appears to impose various degrees of protective inhibition altering profoundly behaviour and response. Three phases of cortical inhibitory activity may appear before the total collapse phenomena already discussed supervene. The first is an "equivalent" phase, when all stimuli produce the same response instead of larger stimuli having more effect than lesser ones. The second is a "paradoxical" phase of cortical activity, when small stimuli produce a greater response than larger ones, the latter now serving only to increase inhibition still further. The third is the "ultraparadoxical" phase, when positive conditioning suddenly becomes negative and negative conditioned reflexes become positive.

Pavlov felt that these various types of inhibitory phenomena helped to explain hysterical and other abnormal behaviour in man. Ample confirmation of his findings was afforded clinically by our experiences with acute battle neuroses in the last war. Temporary breakdown occurred in many normal persons as a result of the intensity and continuity of stimuli that are rarely encountered in peacetime. A near-by bomb explosion, for instance, might produce just such uncontrolled states of excitement as Pavlov described, and also excellent examples of both focal and generalized states of paradoxical and ultraparadoxical cortical activity. Final stupor might also intervene. Thus hysterical paralyses and amnesias became much more common than in peacetime, and in these it was often seen that the more the individual struggled to regain normal function in these states the more inhibited he became—a good example of paradoxical cortical activity. The slow injection of sodium amytal, which in the right dose seems to relieve such inhibitory activity of the cortex, would often restore to normal function a limb or memory as soon as its effects began to work (Sargant, 1942).

Reversals of Behaviour Pattern

Temporary complete reversals of behaviour pattern, in which positive conditioning became negative and vice versa, are also commonplace in severe psychiatric illness in civilian practice. Gordon (1948) has quoted numerous examples in schizophrenic patients. As positive conditioning becomes negative, ideas previously

scorned may become suddenly acceptable, previous emotions of pleasure those of disgust, friends become enemies, and so forth. Pavlov suggested that an individual's thoughts can also become projected on the outside world during such abnormal states of cortical function. Another powerful mechanism brought into play once hysterical behaviour has been produced is an increased state of suggestibility. Confirmation of this is seen in hypnosis, and in the acceptance of the wildest improbabilities by those subjected to excitement or fear and exhibiting other evidence suggestive of cortical inhibitory phenomena.

A final set of observations particularly relevant to our problem was the means of breaking down those with stable nervous systems who were not unduly upset by excessive stimuli or conflict situations. Some animals proved remarkably stable under all sorts of experimental stresses. Patterns of behaviour might be disrupted only when physical debilitation or castration, for instance, had weakened their nervous stability for the time being. When such measures had to be used, the new patterns implanted proved some of the most difficult to remove again later after the animal had had time to adjust to castration or recover from the debilitating process. They could persist despite all efforts to alter them. This was attributed to the basic nervous strength of the animal, which now helped the perpetuation of the new patterns.

A similar precipitation is also seen in humans, producing unremitting types of obsessional and paranoid states. It is most likely to happen in previously stable personalities subject to stress during the menopause, after early removal of the ovaries, following a debilitating illness with severe loss of weight, or after drastic operative procedures. Prolonged nervous stress and exhaustion can also bring it about, and patients can often describe the exact time and date when symptoms became implanted and have persisted ever since.

Psychiatric Treatment Observations in Man

Modern methods of psychiatric treatment must also be studied, as they are very relevant to our problem. In mental illness we are faced with persons who have adopted patterns of behaviour and thought which must often be changed to diametrically opposed ones. This is necessary so that delusions can be removed, ideas of guilt lessened, and basic drives directed into new and more profitable channels. And it is interesting to find that in recent years psychiatric treatment has undergone startling transformations. Intellectual argument and moral exhortation, used as treatment in their own right in the last century, have been increasingly abandoned, as in most severe forms of nervous and mental disorder they are without much effect.

The nervous system of the patient is now much more likely to be subjected to a variety of insults, both psychological and physical, because then better results seem to be achieved from the various forms of psychotherapy also given. Sometimes, for instance, in psychoanalysis the patient is placed on a couch daily and over the course of months or years is subjected to a process in which childhood fears, adolescent panics, previous guilt feelings, and as many past sources of terror and frustration as can be endured by the patient are brought to the surface by a process of "free association" directed by the therapist towards these experiences. As the analysis proceeds emotional storms mount and the patient becomes more and more sensitized to the analyst. Transference situations, both positive and negative, begin to be built up. Physical debilitation may occur in the early stages of treatment because of the anxiety deliberately aroused. Finally a stage is reached when "resistance" to the particular psychotherapist's interpretation of the patient's symptoms is overcome. Possibly far-fetched explanations are at last believed in and acted upon by the patient.

These explanations would generally have been totally unacceptable prior to treatment and often diametrically opposed to previous beliefs. Many of the individual's patterns of behaviour may also be destroyed under this process, allowing new ones to take their place. These changes are consolidated so far as is possible, and behaviour is made consistent with the new "insight" gained. As one patient personally analysed by Freud reported: "For the first few months I was made to feel nothing but increasing anxiety, humiliation, and guilt. Nothing about my past life seemed satisfactory any more, and all my old ideas about myself seemed to be contradicted. When I had got into a completely hopeless state he then seemed to start to restore my confidence in myself and to piece everything together in a new setting."

Psycho-analysis may take longer to bring about what other more violent methods may sometimes achieve in a shorter time. During the recent war, for instance, patients admitted with battle neuroses had often had the first stage of disruption brought about by their experience prior to hospital admission. New stereotypies of thought and behaviour of an undesirable type might also have become implanted in the nervous system. An arm might jerk convulsively and repeatedly, or the mind be fixed on a past experience which could not be divorced from the terrifying emotions that had accompanied it originally. Such conditions might be dispersed by quite crude forms of abreaction. Thiopentone would be injected or ether inhaled. While under the drug an incident or series of incidents of a terrifying or rage-producing nature would be sought for by the therapist, who would deliberately concentrate on such experiences and try to produce as violent an emotional explosion as possible. It was found that it was not always the experience abreacted that produced the best results in all patients, but often the amount of crude emotion that could be released.

A Link with Pavlov's Experiments

This important finding, which seemed to link abreaction with Pavlov's experiments, helped to stimulate this study (Shorvon and Sargant, 1947); for some patients might remember and emotionally relive a disturbing incident with no therapeutic effect. If, however, during a subsequent abreaction, excitement of a much greater degree of intensity could be aroused about the same experience, and emotional release was forced to a point in which the patient showed sudden collapse and temporary cortical inhibition, relief might be immediate. The patient would say his head had cleared suddenly and he felt freed from his fears. He could think about terrifying incidents without experiencing the emotions previously associated with them. We seemed, in fact, to be seeing the same abrupt break-up of recently implanted conditioned behaviour patterns as had occurred in some of Pavlov's animals after the Leningrad flood.

The two most disruptive emotions, and those producing the best effects from a therapeutic point of view, proved to be terror and anger. If terror incidents failed to produce sufficient excitement, another might be sought about which the patient could be stimulated to release great aggression. Several persons would sometimes be needed to control the patient while the explosive outburst of anger was maintained, till he fell back on the couch exhausted and inert. The best results were obtained in those whose abnormal patterns had only recently been implanted. Repeated abreactions might be necessary even when such terminal collapse phases occurred. If only excitement was released, longer courses of treatment were generally necessary. Dull and unemotional recitals of previous traumatic events were nearly always without therapeutic effect.

Few attempts were made to alter a patient's original beliefs and outlook by these methods. Our efforts were directed towards restoring as far as possible previously established attitudes by destroying more recently acquired ones. But, as treatment proceeded, a growing transference between the patient and the therapist generally occurred, with the more ready acceptance of new viewpoints and a temporary increased state of suggestibility. Some psycho-analysts actually used this short-cut method during the war to gain acceptance by their patients of their own particular doctrinaire conceptions of "insight." But equally good results were possible if other types of indoctrination were substituted.

Both the psycho-analytic method and drug abreaction have limited applications. They will be found most effective in persons with a fair degree of previous stability who under stress produce predominantly inhibitory types of symptomatology such as depression, amnesia, paralysis, indecision, excessive fatigue, poor concentration, and other hysterically flavoured symptoms. It seems that this tendency to develop abnormal inhibitory patterns of nervous activity under stress can also be used for their relief in treatment.

Neither method will be found so effective in chronic, strong, and persistent states of anxiety and tension without hysterical overlay, nor in the obsessional neuroses. In these a quite different response to attempted abreaction is obtained. Increasing excitement generally leads not to terminal switch-over to cortical inhibition and collapse but to a state of increasingly uncontrolled excitement. If treatment is pressed, mental confusion results which may require temporary admission to a mental hospital. Neither the same suggestibility nor acceptance of new interpretations of symptoms results from treatment. Moreover, on examining the past history of such patients they show little evidence of past inhibitory activity being primarily responsible for their troubles. On the contrary, they seem to have lacked normal powers of repressing past traumatic experiences. Unable to forget like normal persons, they may remain for years in a continued state of excessive excitation over past incidents. We are probably faced with a quite different pattern of nervous activity in such persons.

In deep states of depression a different picture also prevails. When abreaction is attempted emotional release can rarely be stimulated by psychological means or the use of chemical aids. The individual is so deeply inhibited and retarded that thought may be confined to one topic, and appetite, bowel movement, salivary secretion, and facial expression all lack mobility as well. Positive conditioning may have become negative, and vice versa. However, substituting an electrically induced convulsion for a psychologically induced abreaction, and giving a series of these, can produce truly dramatic results. Thought rumination is dispersed; recently formed attitudes lose their hold on the patient, and older-established patterns of thinking are restored with the abolition of those often diametrically opposed to them which supervened during the illness.

It may not be without significance to our problem that both abreaction and convulsion therapy can be most effective when a state of nervous excitement is produced one way or another in the nervous system and carried on to the point when total cortical inhibition supervenes temporarily, just as in the Leningrad flood experiments, and that such treatments are less effective when severe tension, and not hysteria or depression, constitutes the clinical picture. Normal persons seem to respond to severe stresses by developing more mixed hysterical and depressive reactions than pure tension states when total breakdown finally occurs. Thus history records the rediscovery of the value of abreactive techniques in times of war, pestilence, and disasters of all kinds. In the Middle Ages a violent form of dancing was employed till the depressed person, being stimulated to a crescendo of excitement, finally collapsed in exhaustion. In 1565 Matthioli reported that extra musicians would sometimes have to be employed so that such dancing could be kept going up to its therapeutic endpoint (Hecker, 1844).

Modern Psychiatric Methods

It is not possible to discuss all the modern psychiatric treatments which seem to include evidence of a similar mechanism in their total action. The induction of hypoglycaemic excitement by means of insulin, which is carried on till deep coma occurs, is a recent example. If initial hypoglycaemic excitement is not great enough, then electric convulsion treatment given in insulin sopor may produce better results. Meduna has also described a treatment of neurosis by the inhalation of high CO_2 mixtures, another cerebral excitant leading on to coma; and the best results have been obtained, in our experience, in reactive depressions and in hysterically predisposed persons. Older methods, such as ducking- and swinging-stools, the firing off of guns, and other methods of producing terror states in the mentally deranged, would hardly have been used by psychiatrists of the past if good results had not sometimes occurred. Case selection has obviously been at fault in many instances.

We now know that ideas, and abnormal emotion centred round them, can in fact become so deeply rooted and fixed in the nervous structure of the brain, and accompanied by so much persistent excitation, that relief is finally obtained only by sectioning certain brain tracts, as in leucotomy. Even after operation the ideas may persist unchanged, but with the abolition of continued emotional reinforcement they may gradually lessen or become less of a burden to the patient (Sargant and Slater, 1950).

Loss of weight is often the precursor of breakdown. During the war this was very noticeable in those who began to show new abnormal types of response to stresses that had previously left them unmoved only after the loss of up to 30 lb. (13.6 kg.). Once such abnormal reactions got established they might be difficult to alter again simply by restoring physique, though the development of new ones was minimized. Psychiatry,

however, has only just begun to re-explore the planned use of debilitating procedures in an attempt to dislodge undesirable patterns of behaviour previously established. One successful example, however, may be the recently developed conditioned aversion treatment of alcoholism.

To cure compulsive drinking, not only has a pattern of nervous activity to be destroyed but a change of outlook should also be brought about to help to sustain a future life of teetotalism. The induced vomiting which helps to build up a conditioned aversion to alcohol can be used to produce other effects. The individual can be debilitated and progressively weakened by it. As the treatment proceeds, reversal of previous attitudes and suggestibility may become much more pronounced. A phase amounting to a conversion state may occur about the third or fourth day in a drastic treatment programme. This is the time when new ideas can also be implanted with much less resistance than previously. During the phase of induced suggestibility the most resistant patient may also be persuaded for the first time to consider joining Alcoholics Anonymous as a stabilizing follow-up procedure (Williams, 1951). But only reasonably stable persons who also show stability in their compulsive drinking habits can be helped by this short-cut method. The unstable psychopath has no stability to return to when his drinking is removed, and he invariably relapses.

Preliminary experiments have now been started towards applying variations of this technique to chronic tension states and obsessional neuroses, which prove so resistant to ordinary abreactive techniques and shock therapies because the strong excitation aroused does not readily switch over to inhibition. Repeated doses of apomorphine appear to lower tension profoundly, increase inhibition, and may induce a more suggestible frame of mind in some patients. It is too early to speak of results. But what has already been found is the toughness of the nervous system of some patients, confirmed by their response to other treatments. Apomorphine given four-hourly, with only glucose drinks, can bring some patients to the point of collapse in 24 hours. Yet a female patient, persistently anxious and ruminating on incidents that occurred two years previously, and whose illness had not responded to psychotherapy, abreaction, or E.C.T., was also unmoved by two days' apomorphine treatment. She was slightly shaken by four days of vomiting, with glucose drinks as her only intake. It finally needed another course of seven days' continued vomiting and debilitation before physical and mental collapse became imminent, her mind freed from some of the force of its obsessions, and leucotomy, at least temporarily, avoided. Nor was she very distressed by the treatment.

Religious Conversion

Carrying our study into a field where for centuries people have been made to accept new standards, look upon their past life as one of wickedness and sin, and achieve sudden reorientations of thought and action, we find much to confirm the importance of some of the observations so far reported. Furthermore, we may learn much more about the possibilities of the implantations of new beliefs as well as of destroying others.

During a year spent in the U.S.A. in 1947–8 it was possible to witness some of the more violent forms of conversion practised there, examples of which were also fairly common in Britain up to a hundred years ago. Three different religious groups visited were found to use the same underlying method, differing only in minor points of technique and selection of suitable forms of disruptive excitation. One group at Cincinnati relied on noise, group excitement, and continuously repeated exhortations by evangelists working in relays, also helped by those who had already attained conversion. Twenty to forty persons, coming forward from a large congregation, might be seen kneeling along a rail. As one or other of them showed signs of responding to the excitement going on around them, or the impending transition into the stage of mental dissociation or collapse, he or she would be selected for special attention by the group in an effort to complete the process before passing on to another.

The final stage might be accompanied by an incoherent and abreactive type of jargon sometimes called "the gift of the tongues." It was also interesting to find that the production of sudden total collapse phenomena is referred to by this group as "wiping the slate clean." In the absence of alternative physiological explanation, the victims, experiencing an overwhelming emotional upheaval and often a feeling of having been changed in some unaccountable way, accepted suggestions that these happenings had been brought about by the Holy Ghost. With suggestibility temporarily enhanced, they were the more ready to try to accept a new way of life.

Evangelists with whom this matter was discussed had learnt by experience the desirability of achieving an endpoint of this type if rapid alteration in a person's outlook was to be accomplished. They also tried to distinguish between the genuine and the purely imitative types of emotional release and dissociation copied from others. They were prepared to battle night after night with a potential convert till they considered the genuine phenomena had been brought about or the attempt had to be finally abandoned.

Poisonous snakes (tested and found to be genuinely so in later police court proceedings) were used by another group in Durham, North Carolina. Passed from hand to hand by those already having faith, the snakes were employed with great effect to hasten the production of convulsive states of excitement and dissociation when brought towards others in states of mounting tension and excitement. Profound autonomic disturbance was witnessed in some of the persons, and the end phase of exhaustion and collapse could be dramatic and abrupt. With such methods a state of stupor lasting hours or even days might occur, the convert finally emerging with a new outlook, or at least much more ready to accept one.

A negro group, also studied in Durham, N.C., employed jitterbug dancing as an effective excitant. A small space for this dancing was available in the church for those who were stimulated to it by mounting noise, excitement, rhythmic beating, and singing. They danced singly or in groups, and continued for up to three hours on and off until mental dissociation or collapse supervened. During this time they were subjected to exhortation and repeated simple statements about the beliefs desired of them.

Fasting was also employed in those resistant to conversion. Up to nine days on bread and water in a prayer-room, or complete fasting for up to three days before attendance at a faith-healing meeting, was reported. A negro parson who was asked about this

could only say that he found some people believed more easily on an empty stomach. An evangelist was met who had attained his own sudden conversion experience some years previously in a Georgia prison only while working on a chain gang and debilitated by wet beriberi.

No follow-up of the results of the methods seen could be made in the time available. But the literature on religion shows many stable conversions by such methods, besides instances of repeated backsliding and failures. Normal persons in a temporary state of conflict are more likely to achieve the stable conversions, however, than the constitutionally abnormal, provided a means of disruption can be found which is acceptable in its presenting form and the pressure exerted great enough.

As in psychiatric practice, depressions were seen in which the method had failed because no abreactive release could be produced, but which nevertheless responded satisfactorily to later electric convulsion therapy. One such patient had twice been relieved of depressive attacks by attendance at such meetings, but needed E.C.T. in a later and severer attack of depression. Such meetings also provided their quota of persons who had to be admitted temporarily to mental hospitals in states of excitement or suicidal depression. The precipitation of schizophrenia in a predisposed person was also seen. In fact, the results were comparable to those seen with too indiscriminate a use of modern shock and abreactive treatments, and probably in others subjected to the conversion techniques practised in the prisons behind the "iron curtain."

Sudden and abrupt reversals of behaviour occur which seem akin to the paradoxical and ultraparadoxical cortical activity described by Pavlov and seen in acute war neuroses. People report an overwhelming desire to love their enemies, the loss of fear of previously feared objects, a revulsion against old habits, a pathetic eagerness to embrace people and things previously despised. Furthermore, many become obviously sensitized to the agent of their disruption, the preacher often taking the place of the modern psycho-analyst in this respect.

Modern psychiatry has only recently realized the importance of group factors in therapy, a fact long ago appreciated by the experts in conversion techniques. John Wesley's alteration of the habits of large numbers in various parts of England in the eighteenth century was due to the fact that he found the initial breaking-down process and "instantaneous" conversion aimed at was only the first stage towards stable reorientation. Once conversion had been achieved in large meetings, the converts were split up into groups of no more than 12, who met once a week to talk over difficulties, deal in detail with their problems, and with a "class leader" continued their indoctrination. A snowball effect was created by the larger meetings obtaining the new converts, and so enlarging the number of smaller groups for indoctrination; and a centralized leadership was maintained through the appointed evangelists and class leaders. The small groups could also be used to exclude the undesirable convert, who became well known to his group in their subsequent private weekly meetings. People with dogmatic beliefs themselves obtain greater success with such methods because they are more sure about what they wish other people to believe. In modern psychiatry it also proves easier to implant authoritarian beliefs, such as are provided, for instance, in the Freudian discipline; and presumably a similar state of affairs exists when Marxian dialectics are involved in a conversion process.

Conclusion

Though only one aspect of a very complicated problem has been emphasized, this study suggests that simple mechanistic principles possibly underlie many old and new methods of altering the thoughts, beliefs, and actions of men, though many different explanations have been given of them when used in various cultural settings. Results will depend on the types of nervous system subjected to such methods and the methods selected being acceptable to the person concerned in his particular culture or applicable to the circumstances in which he finds himself placed. Beliefs implanted may be true or false. The most "normal" persons—using our present concepts of normality—are generally those who condition smoothly and correctly to the changing habits and beliefs around them. Others who do so with difficulty, or are constitutionally unstable in a variety of ways, are more difficult to change or stabilize in later life.

When it is necessary to break up already fixed patterns of thought and behaviour intellectual argument alone is often ineffective. Emotions may have to be aroused to act as the initial disruptive agent, and to create, if possible, special states of brain activity conducive to reversals of old patterns or the more ready implantation of new ones. Examples given in this paper show such methods in some of their relatively simple forms. More subtle techniques are also available for the same purpose, probably aided by the same mechanistic principles.

Just as general medicine has advanced by abandoning abstract philosophies in favour of discovering more mechanistic approaches to alterations of bodily function, so a closer study of the mechanics of brain function may teach us about more effective ways of altering a man's thoughts and actions.

REFERENCES

Frolov, Y. P. (1938). *Pavlov and His School.* Kegan Paul, London.

Gordon, W. W. (1948). *J. ment. Sci.*, **94**, 118.

Hecker, J. F. C. (1844). *The Epidemics of the Middle Ages.* New Sydenham Society Translation, London.

Magnus, P. (1939). *Edmund Burke.* John Murray, London.

Pavlov, I. P. (1941). *Conditioned Reflexes and Psychiatry.* Lawrence and Wishart, London.

Sargant, W. (1942). *British Medical Journal*, **2**, 574.

—— (1948). *Dig. Neurol. Psychiat.*, **16**, 193.

—— (1949). *Proc. roy. Soc. Med.*, **42**, 367.

—— and Shorvon, H. J. (1945). *Arch. Neurol. Psychiat., Chicago*, **54**, 231.

—— and Slater, E. (1950). *Proc. roy. Soc. Med.*, **43**, 1007.

Shorvon, H. J., and Sargant, W. (1947). *J. ment. Sci.*, **93**, 709.

Williams, L. (1951). *Brit. J. Addict.* Awaiting publication.

The production of plastic lenses has greatly increased in recent years, and they are said to have certain advantages over ordinary glass lenses; they are safer in many ways, and if they did not scratch so easily they might well replace glass ones (*Vision*, Vol. 5, No. 2). They are indistinguishable from glass in appearance, and are about half the weight; as they cannot splinter, they are very suitable for use in rimless spectacles. Generally speaking, vision is clearer, because plastic lenses absorb less light. Since plastic is softer than glass, they are more liable to surface scratching, but unless the mark is very bad it makes practically no difference to the wearer, as there is no sharp reflecting edge to deflect the light. The raw material from which these lenses are made is a synthetic plastic, methyl methacrylate.

EXPERIMENTAL PSYCHOSES AND OTHER MENTAL ABNORMALITIES PRODUCED BY DRUGS*

BY

W. MAYER-GROSS, M.D., F.R.C.P.

Director of Clinical Research, Crichton Royal, Dumfries

The systematic use of drugs for the production of "artificial psychoses" dates from the early work of Kraepelin (1883). A new insight into abnormal mental states is achieved by the subject's observation of his own mental experiences. Kraepelin mentioned this project in 1892 in an introductory paper opening a series of investigations of the effect of drugs on some elementary psychological functions. Thirty years later he wrote a kind of epilogue to this part of his work (Kraepelin, 1925); he stated that the results were disappointing and discouraging, because the method did not succeed in arriving at a generally recognized psychological interpretation of psychic functions. If this had been the only aim, one could to some extent agree with this condemnation: some obsolete ideas of association psychology when applied to experiments with alcohol, coffee, morphine, tea, etc., have proved open to criticism and have not been very fruitful for psychiatry.

On the other hand, experiments with mescaline, hashish, ether, nitrous oxide, cocaine, and similar chemical substances which produce excitation of the central nervous system and symptoms comparable to those in psychoses have led to interesting results which are worthy of reconsideration in the light of present-day problems. This work is not yet complete and so is not ripe for an epilogue. New drugs are still being discovered and tried out.

The father of the method is Moreau de Tours, who in his monograph *Du hachisch et de l'aliénation mentale* wrote in 1845: "By its mode of action on the mental faculties, hashish gives to everyone who submits himself to its strange influence the power of studying, on himself, the moral disturbances of mental illness, or at least the principal intellectual disorders from which all kinds of mental disturbances originate." At this time the *Confessions of an English Opium Eater*, by de Quincey, had appeared and Davy had published his striking observations under the influence of laughing-gas.

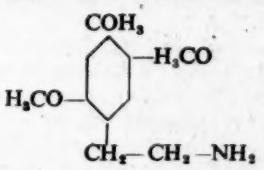
Mescaline

Kraepelin was not only interested in the action of drugs on certain elementary functions; he was equally keen to determine the *specific* change in mental activity which he assumed each chemical substance to produce. With this in view, he initiated experiments with mescaline by Knauer in 1911 (Knauer and Maloney, 1913). Another of Kraepelin's pupils, Wilmanns, organized the Heidelberg experiments and was responsible for Beringer's work in this field, from which some passages are quoted later.

The problem of the specificity of the mental picture following the taking of a certain drug is that of the wider issue of chemical constitution and pharmacological effect. As many of the drugs hitherto employed for psychiatric experiments are time-honoured intoxicants, used in different parts of the world as stimulants for religious and social purposes, there seems to be a large unexplored field in which a systematic search for substances with such central effects would certainly be worth while. The recent chance discovery of lysergic acid diethylamide, the most powerful of all "phantastica" known so far, seems certainly to confirm this challenge to the pharmaceutical chemist.

To add a few more data from the intriguing history of these drugs is a temptation difficult to resist. Many have a considerable anthropological and cultural significance. Cannabis indica addiction, with its wide distribution in the Middle East, including Greece and other parts of Asia and Africa, and its varied modes of intake through the ages and in different countries, could be the subject of a monograph by itself. A few remarks on mescaline, its origin and discovery, may serve as an illustration. The pharmacologist Lewin found it in wide use as an intoxicant to produce ecstatic states for special religious occasions among Red Indian tribes in Mexico and in North America near the Mexican border. He identified the mescal buttons chewed by the Indians as parts of a cactus plant. Inquiry into early reports disclosed that the drug had already been mentioned in the description of this part of Mexico by Sahagun early in the sixteenth century, and that the "prophetic" quality of peyotl, the native name of the prepared cactus, was probably known to Aztec medicine before the conquest of the country by Cortez.

The chemistry of the active principle in peyotl was studied and largely explained by Heffter in 1898. According to Spaeth (1918) mescaline is 3, 4, 5-trimethoxyphenylethylamine, with the formula:



Anthropologists, such as Lumholtz (1894) and Mooney (1896), collected descriptions of the poetic and colourful mythus and elaborate ceremonies practised among the Indians when gathering, preparing, and administering the drug. Thanks to the commercial skill of exporters, the use of the drug spread around the year 1900 from the Mexican frontier to several Indian tribes in the reservations of North America. What was originally a pagan rite—peyotl was considered God-like—was incorporated into the Christian liturgy of Indian groups who had been converted long before but were still ready to revive old tribal customs by chewing the mescal buttons at the time of festival gatherings. They now interpreted their ecstatic and hallucinatory experiences according to Christian ideas. The use of the drug was, and probably still is, a problem for Christian missionaries, who insist that its regular intake leads to increasing laziness and impairment of will power.

Returning to the topic of scientific study, the first self-experiments with the drug were carried out in America by Prentiss and Morgan (1896) and by Weir Mitchell (1896), who gave a description of colourful visual hallucinations. One year later, Havelock Ellis published a note on the phenomena of mescal intoxication which consisted of a graphic description of one self-experiment. The article seems to have attracted little attention, probably because it was obviously regarded as the product of an artist-writer's wild fantasy.

*From a lecture delivered at the Institute of Psychiatry, Maudsley Hospital, London, on February 15, 1951.

Clinical Picture of Mescaline Intoxication

It should be realized that the outward behaviour of the subject acutely intoxicated with mescaline is relatively normal. He may be absorbed in his experiences, and will talk about them freely but rationally. Only if the intoxication has become extreme may he lose control of himself and sink into a sleep-like sopor or delirium.

Hashish, in contrast, produces much more restlessness and movement at an earlier stage; mescaline invites passivity and rest. Hyperkinetic states, sometimes with a choreo-athetotic or other organic appearance, such as catalepsy and muscular rigidity, are frequent in hashish intoxication but rare under mescaline.

For the *mental state*, I quote from one of my own self-descriptions published by Beringer (1927).

"I received two subcutaneous injections between 9 and 10 in the morning. They first produced slight nausea and local pain, soon followed by difficulties in concentration on useful work. A general feeling of pleasant carelessness with slight fatigue took hold of me, but still with a background of sickness. At about 11 a.m. changes in the *colour* of objects were noted and the increased intensity of after-images became disturbing. With closed eyes visions of moving constantly changing patterns appeared and attracted the whole attention: Oriental tapestry, mosaic-like wall-papers, kaleidoscopic coloured geometric patterns, lines in brilliant luminescent colours or in black-and-white, etc. The colours were sometimes dazzling and gaudy, as in some Continental rural art, and shortly afterwards there were tender pastel shades. The colours of real objects appeared more pure, more clean, untarnished by dirt, then a moment later everything seemed vague, remote and veiled, not quite real.

"Meanwhile, *euphoria* heightened into a feeling of superiority and joviality; I was ready to joke about everything, and especially to sneer at some psycho-physical tests and at the people trying to test me.

"While in a dark room, I rested between wakefulness and sleep. Pulling my right ear-lobe, I realized that this was the only part of my body still present. My whole body feeling was concentrated and had its seat in the ear-lobe, which I was holding much enlarged in my hand. Opening my eyes and seeing the room, I was soberly aware of the real situation. There was, however, a marked tendency to *think in visual images:* I pondered over my present level of consciousness, which at once appeared before my eyes as the water level of a harbour with sailing boats, flags, and sunshine. Connexion between this picture and my thinking was self-evident and fully convincing. On another occasion, when thinking of domestic affairs, I had the image of a ceiling or vault entirely made of knitting in grey wool. There were also visual hallucinations unconnected with my conscious thinking, especially friendly animals, little demons and dwarfs, fairy-tale ornaments and mythology from the aquarium such as one sees sometimes on the walls of inns. The faces of people around me were slightly distorted as if drawn by a cartoonist, often with the emphasis on some small humorous but nevertheless rather characteristic feature.

"Jollity and mirth persisted for some time, often mixed with a Swiftian feeling of irony expressed without much reticence or self-control. My remarks were objectively not at all as strikingly witty as I thought them at the time.

"This mood was replaced in the course of the afternoon by an entirely different one: the change began with a bodily feeling of being *cold*. The coolness was not so much of the body surface, although feet and hands were cold too, but seemed to come from inside the limbs and the trunk. A certain restlessness was felt to be the response to increasing waves of cold. The state was not unpleasant and did not sober me up; on the contrary, I continued daydreaming and delighted in changing images illuminating my present condition. One picture, a huge dome of concrete supported by an iron construction, impressed me deeply. I imagined myself inside this dome, and was proud that I understood its beauty so well. It was the perfect representation of my emotional condition, which was far away and completely detached from all the small idyllic things of the little-valley-with-mill type which I like so much in ordinary life. Music of the mouth-organ was offensive; I wanted a symphony orchestra or the organ of a large cathedral. I remained, however, entirely myself, and did not lose my identity. The bodily feeling of cold was like a sting which made the enjoyment of the mental state an even greater treat. On the other hand, there was little progress of thought in this condition: it was a purely *passive* attitude in which I tried to relish and taste to the full this experience, which seemed so important and unique that I took great pains to describe my extraordinary feelings to the observing colleague. . . ."

The impression, from this description, that mescaline necessarily produces enjoyable and unusual experiences, is somewhat misleading. This may be shown by some excerpts from the report of another subject of the same series of experiments, a well-known scientist:

"A most unexpected observation made me laugh, and I exclaimed, 'This is all terribly tasteless.' I see and feel myself in the same position as I was before, lying on my back, the arms crossed over my chest. My right arm is a street with a group of toy tin soldiers. My left arm goes across the street like a bridge and carries a railway. I feel myself like a giant, like Gulliver—but the whole thing is depressing because the toys are terribly common in form and colour; but I feel I myself *am the vision*. . . . In the depth of the intoxication I don't feel well and feel inferior. I tell myself it is an experiment. I know that I soon will get out of this condition. As a continuous state it would be horrible.

"My right shoulder is a hill, and from this highest point the coast flattens out towards my feet. My head forms the right upper corner of the picture. I feel that I am a large scenery, and I see mountains, towns, villages, and the sea behind me, but if I look closer it all is unreal, not really sharp, like cheap prints. The whole thing is unsatisfactory, and I am waiting for something better to come."

Some Important Symptoms

These observations serve to illustrate the characteristic psychopathology of the intoxication, some symptoms of which deserve special discussion.

Predominance of Visual Experiences

The predominance of visual experiences in the picture is striking—not only on account of the persistent visual hallucinations and illusions, but by the impressiveness of seen real objects, their shape and colour: visual images replace thinking and express feelings and moods. Only the tactile senses and the body-image sensations seem to compete with vision at times. When Zador gave mescaline to a patient who had been blind since the age of 2, he became hallucinated in the sphere of the body-image only. Generally speaking, mescaline is the drug of the visionary, and it was probably for this reason that it was so readily accepted for religious use.

Movements of Objects

Within the field of vision the drug interferes with the stillness and movements of objects. The remarkable mechanism by which we normally see things fixed and of persistent shape seems to break down in the intoxication. The process of perceiving and of picturing

our surroundings at an instantaneous glance is disturbed, probably slowed down, and we observe the "scanning" of the picture in progress.

"Looking at a pattern of triangles and dots on the cover of a book, I saw the triangles changing their shape, becoming higher and more pointed, wider and more obtuse; they came out of the paper as though plastic and then withdrew into it. At the same time the whole pattern was in movement. Also the dots were in steady movement away one from another and from the triangles. . . .

"On a printed page of a book I saw the lines of print in quick movement running away from left to right; later they moved in the opposite direction, also towards one another, each letter constantly changing shape and size. The same persistent movement was seen in the changing visual hallucinations, but there were also periods of complete standstill."

Imaginary movement of this kind is obviously related to the creative play of imagination as described by artists of genius, such as Leonardo da Vinci and Goethe, but also by Johannes Mueller, the father of modern sensory physiology. One of Beringer's subjects reported as follows:

"On a whitewashed wall there is movement of grey and white lines apparently at different levels, horizontal and vertical, forming a lattice-work, moving from left to right, behind it the formation of a picture while the movement continues. A larger shady spot becomes a house, like a castle with windows, entrance, drive from the gate, a pond in front, the castle mirrored in the water; behind the castle a mountain range, slow-moving clouds in the sky—the picture is in constant change, new lines becoming more marked and starting an entirely new design. The new design expressed itself clearer and when it was fully developed something different was slowly started. Deliberate intention, independent of the basic material of lines, the will to imagine something entirely different, had no effect."

In this connexion, experiments with the widely used Rorschach ink-blot test are worth noticing: the results revealed little of the personality background, but were mainly influenced by the symptoms of the intoxication (Bleuler and Wertham, 1932). In one case only was the personality more truthfully revealed under mescaline than in a test given beforehand without the drug.

Disorders of Time

Closely linked with the disturbed visual appreciation of movement, but not identical with it, are the frequent disorders of time experienced in mescaline intoxication. They vary a great deal from case to case, but a slowing down of the passage of time, sometimes culminating in a standstill or complete timelessness, is often described. The vortex of kaleidoscopic colours turns without time. Some experiences of heightened insight seem of eternal duration. Time may be discontinuous and fragmented, as in the case of one subject who tried to imagine the stages of the way from the hospital to his home. He made only very slow progress: the different stages of the journey, which ordinarily took 20 minutes, seemed to go on without end; moreover, the stages appeared disconnected, like a series of snapshots. The basic time grid seemed to have broken down.

Synaesthesiae

Among the striking phenomena of the intoxication the interrelations of sensory experiences in the form of synaesthesiae are of special interest. As visual perception prevails, the influence mainly extends from other senses to vision: the knocking of workmen outside the room was accompanied by hallucinatory dots of colour in the air; with each stroke of the clock more red spots appeared in the coloured pattern, etc. But synaesthesiae between other senses are also experienced. The following report of a usually matter-of-fact scientist shows the peculiar result of the synaesthetic perception, but also the inadequacy of ordinary language for such experiences:

"One believes in hearing noises and seeing faces, but everything is one. I hear scratching, the sound of loud trumpets, I am the lattice-work. What I see, I hear; what I smell, I think. I am music, I am the lattice-work. I see an idea of mine going out of me into the lattice-work. This is not a metaphor, but the perception of something coming out of me. . . . I felt, saw, tasted, and smelled the noise of the trumpet, was myself the noise. . . . Everything was clear and absolutely certain. All criticism is nonsense in the face of experience. . . ."

State of Consciousness

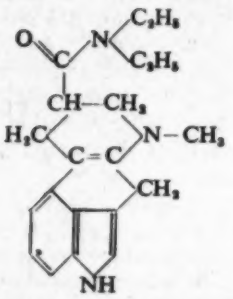
It is difficult to classify the state of consciousness during the intoxication which allows such full self-observation and, at times, seems to foster detachment and self-scrutiny. At other times the same subject seems to have lost all clarity of consciousness, is drowsy and even close to a state of sleep. As for continuity of consciousness, this is at times disrupted and fragmented. Single impressions are dissociated and without connexion, while at other times everything seems to flow in a unified stream of deep significance and importance, and is connected with the whole life of the subject, who identifies himself with the experiences. As for the breadth and capacity of consciousness, these may be narrowed down to one small impression, as in one subject's description that the whole world was contained in a fluff of dark wool on the doctor's white coat.

Relation to Other Mental Reactions

It can be maintained that the symptoms caused by mescaline, as well as those due to intoxication by hashish, cocaine, lysergic acid, and even amphetamine, all belong to the large group of exogenous reactions of which *delirium* is the typical form. The latter may be called one of the basic modes of cerebral reaction (Bleuler, 1944). Differences in symptoms found with various drugs have been attributed to differences in the personality of the intoxicated. This may be true for an early stage or for cases of very mild intoxication. The delirious picture, on the other hand, is probably common to all intoxicants when their effect is most severe. Between these two ends of the scale is a stage in which probably each drug shows certain special features: mescaline produces derealization, followed by visual and tactile illusions in relative clearness of the sensorium; hashish produces special forms of dissociation of thought, with hyperkinesis; cocaine produces mainly auditory hallucinations, with fear, increasing to terror, often with a sexual colouring, etc.

The symptoms of lysergic acid diethylamide appear to be closest to those of mescaline, though its chemical nature differs widely. Its intoxicating properties were discovered by chance by the biochemist A. Hofmann, who had synthesized it from one of the many constituents of ergot which he investigated (Stoll, 1947). If the

chemical constitution of lysergic acid suggested by Jacobs and Craig (1938) is accepted, it has the following formula:



It is much more powerful than most well-known alkaloids, and is effective in about one-tenth of the amount at which adrenaline or thyroxine shows any physiological action.

Symptoms of mescaline intoxication have been compared to those of *schizophrenia*, but it is much more the strangeness experienced by the patient suffering from schizophrenia and the difficulties of describing what is happening in the two conditions which are similar. Many typical schizophrenic symptoms, especially in subacute and chronic states, are never seen in mescaline intoxication. Early psychotic phenomena in acute schizophrenia show certain analogues, especially in the field of hallucinations and other sense abnormalities.

Derealization and *depersonalization*, frequent in schizophrenia, but present also in many other mental illnesses, occur almost regularly after mescaline, if only for a short period. I have recently observed a typical picture of this kind lasting over several hours in a subject after lysergic acid diethylamide. Guttmann and Maclay (1936) suggested small doses of mescaline as an empirical therapy in this intractable condition. Nowadays, when even prefrontal leucotomy has been performed in such patients, it would be justifiable to attempt the production of a severe mescaline intoxication in the hope that the depersonalization may clear together with the other toxic symptoms from the drug.

Results of Experiments

What have we learned from these experiments that could justify their continuation? The subjective experience of an artificial psychosis of this kind is of great value to the psychiatrist, who, without danger, "can live in the strange worlds with which he has to deal in his daily work. He can observe and will be impressed by the oncoming psychopathological symptoms and their recession; he will have a better grasp of much of what his patients report" (Stoll, 1947).

In particular, the problem of *hallucinations* and kindred sensory disturbances has been studied; it was shown that the disordered perceptive system plays an important part in their origin. They are not only uncontrolled imagery released after blocking of higher centres, but may be closely related to quantitative disturbances of the sensory apparatus (Mayer-Gross and Stein, 1926). An attempt was made to extend this principle to the explanation of illusions and hallucinations in psychoses of all kinds; many descriptions of patients reporting bizarre and improbable experiences became better understood in the light of these observations (Mayer-Gross, 1928).

If mescaline was given to a chronic schizophrenic suffering from persistent hallucinations it was found that the patient distinguished the new phenomena and remarked on their appearance, usually laying blame for them on the same persecutors who had molested him before. Patients in a state of delirium, on the other hand, showed an increase of delirious symptoms; they seemed unable to distinguish the mescaline experiences as anything new; they made no comment and reacted in no way differently to them than to other symptoms of the delirium (Zucker, 1930). If a normal subject intoxicated by mescaline was asked to use his visual imagination for deliberately picturing certain objects or past events, it was shown by Zucker and Zador (1930) that the process of imagery was interfered with by the drug.

Zador (1930) has also studied the influence of mescaline on the phantom limb of limbless patients and on cases of blindness due to differently localized lesions. The phantom limb as a recently acquired part of the body image was earlier and much more affected by mescaline than the rest of the body. The visual phenomena produced by the toxic condition were more or less identical whatever the origin of the blindness—injury, glaucoma, optic atrophy, tumours of various locations—but the degree of vividness and persistence of visual sensations was definitely related to the duration of the blindness. For instance, if one eye had lost its function later than the other, visual hallucinations were more marked or appeared exclusively in the eye that had lost its sight later. Altogether, the hallucinatory phenomena of blind subjects were, as one would expect, more frequent in sensory fields other than the visual.

Mechanism and Causation

By what mechanisms, chemical or physical, or both, are the mental symptoms produced? Where is the point of attack of these drugs in the metabolism of the brain cell, and what can be deduced from their effect about the aetiology of psychiatric symptoms and illness? We might expect that these questions could be readily answered by the results of our experiments. Actually, only partial answers can be given.

Cannabinol, the active principle of hashish, was found by Marx *et al.* (1932) to have a considerable diuretic effect, leading to a concentration of the blood. Its influence on carbohydrate metabolism was also demonstrated and, conversely, its psychological effect was much enhanced by the simultaneous intake of sugar. This agrees well with the Eastern habit of taking sweets while smoking or eating hashish.

Quastel and Wheatley (1933) studied the effect of mescaline and other amines of the aromatic type on the oxidation of brain *in vitro*. They found an inhibition of oxidation similar to that of the narcotics, and this would suggest that the effect could be abolished by succinate. J. R. Smithies (1951, personal communication) reports the successful termination of mescaline symptoms by oral administration of sodium succinate. Quastel and Wheatley suspected that inadequate detoxication of similar substances in the liver may lead to their circulation in the blood, causing mental disorder. Hence the importance of hepatic function for the study of the aetiology of psychiatric diseases.

The more recent investigations on mescaline intoxication by Jantz (1941) seem to point in the same direction. He studied the metabolism and blood chemistry of the intoxicated individual from every aspect. His various findings seemed to point to capillary damage caused by the drug. Through the walls of

damaged capillaries protein leaves the blood, entering the tissue, where it is stored. Jantz confirmed this theory by experiments on dogs. The animals showed nitrogen retention when they received mescaline but massive excretion of nitrogen on those days when the drug was withheld. Pathological studies revealed capillary damage in the liver, a picture described by Roessle under the term of " serous hepatitis."

The comparison of these findings with Gjessing's in periodic catatonia is close, but Jantz mentions it with due caution. His findings certainly need confirmation by other workers.

The intermediary role of the liver as a site of pathology in mental disorders has an unfortunate history in ancient and modern medicine. Its latest abdication was in the field of alcoholic psychoses. Delirium tremens and Korsakoff states, after having been hypothetically ascribed to hepatic dysfunction for many years, are now recognized as due to nutritional deficiencies. The mescaline-like effect of 30–50 μg. of lysergic acid diethylamide taken by mouth makes it very doubtful if the liver has any share in the symptoms of the intoxication.

Future Research

Within the last ten years much has been learned about metabolism of the central nervous system that can be applied to experimental psychoses. We can expect the biochemist to give us more information on the action of these drugs *in vivo*, especially if full use is made of parallel experimental studies in animals. Here histopathological and histochemical methods, which have recently widened the field of investigation in the central nervous system, should elucidate the rather special interference with oxidation which one can suspect to be taking place. Finally, the new electro-physiological methods will have their place in this experimental work. So far the standard electroencephalogram taken in mescaline and other intoxications has not revealed any characteristic changes; but with the new method of carefully dosed stimulation—for example, in the visual field—and with electrodes to record the less accessible and more remote electrical discharges some insight into the action of the intoxicants can also be expected.

References

Beringer, K. (1927). *Der Meskalinrausch*. Berlin (with numerous references).
Bleuler, M. (1944). *Schweiz. med. Wschr.*, **74**, 923.
—— and Wertham, F. (1932). *Arch. Neurol. Psychiat., Chicago*, **28**, 52.
Ellis, Havelock (1897). *Lancet*, **1**, 1540.
Guttmann, E., and Maclay, W. S. (1936). *J. Neurol. Psychopathol.*, **16**, 193.
Heffter (1898). See Beringer, K. (1927).
Jacobs, W. A., and Craig, L. C. (1938). *J. Amer. chem. Soc.*, **60**, 1701.
Jantz, H. (1941). *Z. ges. Neurol. Psychiat.*, **171**, 28.
Knauer, A., and Maloney, W. J. M. A. (1913). *J. nerv. ment. Dis.*, **40**, 425.
Kraepelin, E. (1883). *Philos. Studien*, **1**, 573.
—— (1925). *Psychol. Arb.*, **8**, 181.
Lumholtz (1894). See Beringer, K. (1927).
Marx, H., *et al.* (1932). *Nervenarzt*, **5**, 346.
Mayer-Gross, W. (1928). In *Handbuch der Geisteskrankheiten*, edited by O. Bumke. Allg. Teil, **1**, 427.
—— and Stein, H. (1926). *Z. ges. Neurol. Psychiat.*, **101**, 354.
Mitchell, S. Weir (1896). *British Medical Journal*, **2**, 1625.
Mooney, J. (1896). *Therap. Gaz., 3rd series*, **12**, 7.
Prentiss, D. W., and Morgan, F. P. (1896). Ibid., 3rd series, **12**, 577.
Quastel, J. H., and Wheatley, A. H. M. (1933). *Biochem. J.*, **27**, 1609.
Spaeth (1918). See Beringer, K. (1927).
Stoll, W. A. (1947). *Schweiz. Arch. Neurol. Psychiat.*, **60**, 279.
Zador, J. (1930). *Mschr. Psychiat. Neurol.*, **77**, 71.
Zucker, K. (1930). *Z. ges. Neurol. Psychiat.*, **127**, 108.
—— and Zador, J. (1930). Ibid., **127**, 15.

SODIUM γ-RESORCYLATE IN RHEUMATIC FEVER

BY

J. REID, M.D., M.R.C.P.

R. D. WATSON, B.Sc.

J. B. COCHRAN, M.B., B.Sc., M.R.C.P.

AND

D. H. SPROULL, M.B., Ch.B., B.Sc.

(From the Clinical Chemotherapeutic Research Unit of the Medical Research Council in the Gardiner Institute of Medicine, University of Glasgow)

Salicylate has an established place in the treatment of rheumatic fever, though the dose required for full therapeutic action may also give rise to undesirable effects. A drug with a greater safety margin might improve treatment of rheumatic fever, and this paper describes an attempt to find such a substance.

Our starting-point was the observation that salicylic acid, which is *ortho*hydroxybenzoic acid, has a therapeutic action in rheumatic fever, yet its isomers—the *meta*- and *para*-hydroxybenzoic acids—are inactive (Stockman, 1920). The physiochemical properties of salicylate and its isomers were examined for some essential difference which might explain why the first is effective and the others are not. A notable difference is that salicylic acid is a much stronger acid; this has recently been attributed to its ability to form an additional or chelate ring, a property not possessed by the isomers (Baker, 1936). The chelate or claw-like ring is known to chemists, but is perhaps not so familiar to clinicians. It is formed by virtue of the hydroxyl group of salicylic acid sharing its hydrogen ion with the ketone of the carboxyl group (Fig. 1).

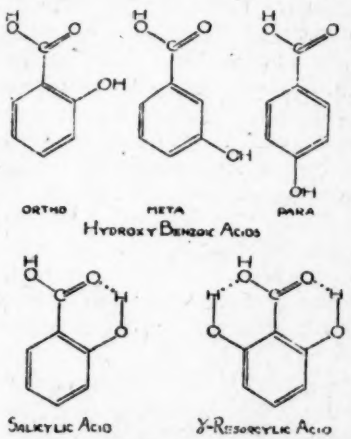


FIG. 1.—Showing the formation of a chelate ring by salicylic acid and of a double chelate ring by γ-resorcylic acid. The isomers of salicylic acid do not chelate because the distance between the hydroxyl and carboxyl groups is too great.

A comparison of the structure of salicylic acid and its isomers shows that the formation of a chelate ring depends on the respective positions of the carboxyl and hydroxyl groups. If the hydroxyl group is in the ortho position, as in salicylic acid, a chelate ring may be formed because of the proximity of the reacting groups to one another. If the hydroxyl groups are in the meta and para positions chelate rings cannot be formed, as the active groups are too far apart (Fig. 1).

If the formation of this special type of ring structure is responsible for the therapeutic action of salicylate, then it might be possible to enhance this action by increasing the chelation effect. This possibility has been explored by investigating the pharmacological properties and therapeutic action of 2:6-dihydroxybenzoic acid, or

γ-resorcylic acid, which was specially selected to test the hypothesis, as it can form a double chelate ring and is in consequence a much stronger acid than salicylic acid (Fig. 1). The mono-sodium salt of γ-resorcylic acid, henceforth referred to as γ-resorcylate, was prepared, and, when animal toxicity tests indicated that it was safe to give to man, its effect in healthy volunteers was investigated and then a preliminary trial of its action in rheumatic fever was carried out.

The purpose of the clinical trial was to compare the action of γ-resorcylate and salicylate in rheumatic fever, and just before this work started Hench and his colleagues (1949) reported the dramatic effect of cortisone and A.C.T.H. in rheumatoid arthritis and rheumatic fever. The general similarity in the clinical, biochemical, and side-effects of cortisone, A.C.T.H., and salicylate in rheumatic fever (Cochran, Watson, and Reid, 1950) seemed to warrant an extension of our work. Pharmacological investigations of the effect of salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, were thus carried out by Professor Buttle and by Dr. Prunty and Dr. Clayton. Their findings will be reported separately. In this paper the effect of γ-resorcylate in healthy individuals and its excretion in the urine after a single oral dose are described and an account of its action in rheumatic fever is given.

Sodium γ-Resorcylate in Healthy Individuals

Eight healthy adult males having the same diet and fluid intake were given single doses of 200 mg. of sodium γ-resorcylate by mouth to investigate the clinical reactions to the drug and to study its excretion in the urine. The dose was given in water at 10 a.m., and urine was collected at two-hourly intervals for six hours, then at the thirteenth hour, and, finally, after 24 hours. A simple colorimetric method for estimating γ-resorcylate in the urine was evolved: 1 ml. urine was made up to 25 ml. with a *p*H 2 buffer and 0.1 ml. of a saturated aqueous solution of ferric chloride added. The presence of γ-resorcylate is indicated by the development of a blue colour, the intensity of which varies with the amount of the substance in the urine. The blue colour is not stable and it quickly turns mauve and then brown, but satisfactory results, as judged by addition of known amounts of γ-resorcylate to urine, are obtained if the colorimeter reading is taken immediately after the iron solution has been added.

No serious reactions followed the administration of 200 mg. of γ-resorcylate by mouth to healthy men; the excretion of the drug in the urine is shown in Table I. Considerable quantities (average 21 mg.) appeared in the urine in the first two hours after the dose, and the average peak excretion (35 mg.) was reached between the second and fourth hours. Thereafter the rate of excretion steadily fell until at 24 hours only small quantities were present. The average amount excreted in 24 hours was 134 mg.—that is, about 67% of the dose given.

TABLE I.—*Urinary Excretion of Sodium γ-Resorcylate by Healthy Males*

Case	Urinary Sodium γ-Resorcylate (mg.) at Intervals after 200 mg. by Mouth					
	0 to 2 hrs.	2 to 4 hrs.	4 to 6 hrs.	6 to 13 hrs.	13 to 24 hrs.	Total mg./24 hrs.
1	19	30	27	45	14	135
2	23	46	36	41	13	159
3	33	60	43	36	18	190
4	13	18	24	34	0	89
5	22	41	37	54	8	162
6	23	33	31	—	—	—
7	18	34	27	10	10	99
8	20	19	24	32	10	105
Range ..	13–33	18–60	24–43	10–54	0–18	89–190
Average	21	35	31	36	10	134

These results indicate that γ-resorcylate is rapidly absorbed and that peak blood levels are probably attained between two and four hours after oral administration.

Sodium γ-Resorcylate in Rheumatic Fever

The effect of γ-resorcylate has been investigated in seven patients with rheumatic fever. All the patients had fever, tachycardia, and a migrating polyarthritis on admission to hospital. Further particulars of the sex, age, and clinical state of the patients are shown in Table II. A standard diet containing 60 g. of protein, 70 g. of fat, 250 g. of carbohydrate, 3–5 g. of salt, and 2 litres of fluid was given to each patient, and the intake of fluid, protein, and salt was checked each day. The output of urine every 24 hours was measured and its nitrogen and chloride content were estimated to allow restricted fluid, nitrogen, and chloride balances to be carried out.

TABLE II.—*Clinical Particulars of the Patients*

Patient	Age in Years	Sex	No. of Previous Attacks	On Admission to Hospital			
				Temp.		Pulse Rate (per min.)	Cardiac Involvement*
				°F.	°C.		
J.H. ..	14	M	1	101	38·3	100	0
J.K. ..	16	M	0	101	38·3	100	0
J.S. ..	44	M	0	102	38·9	100	+
M.McK. ..	14	F	1	101	38·3	98	+
H.McI. ..	13	F	3	101·6	38·7	100	+++
S.M. ..	27	F	0	104·2	40·1	120	0
M.J. ..	12	F	0	102·8	39·3	136	++

* Cardiac involvement was assessed from the general condition of the patient, the size of the heart, the presence of murmurs, and electrocardiographic changes.

γ-Resorcylate was administered by mouth to all patients, and, as we were employing a compound which to our knowledge had not previously been given to man, the dosage had to be arbitrarily chosen and cautiously increased, so that it tended to vary from patient to patient. Six received amounts varying from 1.8 g. in three days to 10 g. in 10 days, an average of 0.8 g. a day. The seventh patient, a man of 16 stone (101.6 kg.), was given the comparatively large dose of 7 g. a day for four days. The total daily dose was usually divided into five equal portions and given at four-hourly intervals, omitting one dose in the middle of the night. The average dose in six patients was thus about one-tenth of the usual therapeutic dose of salicylate. The amount given to the seventh patient was about equal to that of salicylate.

The object of the investigation was to compare the effect of comparatively small doses of γ-resorcylate with the known effect of therapeutic doses of salicylate (1) on acute rheumatic manifestations, such as arthritis, fever, and tachycardia; (2) on the E.S.R.; and (3) on fluid, nitrogen, and chloride balances, which show striking changes during salicylate therapy (Reid, Watson, and Sproull, 1950). The results are described under these headings.

γ-Resorcylate and Acute Rheumatic Manifestations

Arthritis was relieved in one to four days after γ-resorcylate administration in all seven patients. The promptness of relief in three was almost incredible, as a few hours after the first dose was given they were able to move acute joints which had been practically immobile.

Relief in the other four patients was less dramatic in the sense that joint pain continued for two to three days and then suddenly disappeared. However, between the fourth and seventh days from the first dose of γ-resorcylate six of the seven patients had recurrence of muscle and joint pain involving the neck muscles and knee-joints particularly. In five patients pain was not accompanied by swelling and was quickly relieved by movement of the affected part. The sixth patient developed a diffuse painful swelling of both hands. All the fingers were symmetrically swollen and tender, and resembled the appearance in acromegaly. After discontinuing γ-resorcylate the swelling and pain in this patient quickly subsided.

The effect of γ-resorcylate on temperature and on pulse and respiration rates, illustrated in Fig. 2, was not

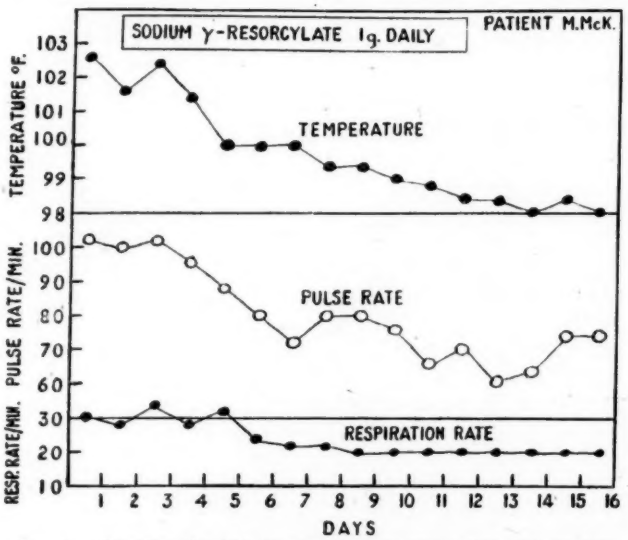


FIG. 2.—Showing the fall in temperature and pulse and respiration rates during γ-resorcylate administration.

quite so spectacular as with salicylate. After a slight initial rise in some patients the temperature and pulse and respiration rates settled gradually in the course of the first five to seven days. The fall in temperature by "lysis" rather than by "crisis" may be due to the fact that profuse sweating, which often occurs with salicylate, was not observed with γ-resorcylate. Other clinical changes noticed after the third day were: (1) Emotional instability and mental confusion in four patients, associated with muscular weakness, myalgia, arthralgia, slight fever, tachycardia, rapid respirations, and a dry tongue. This resembles the "dehydration syndrome" which we have previously described as resulting from overdosage with salicylate (Reid, Watson, and Sproull, 1950). (2) Puffiness of the face in two patients accompanied by acne-like pustules on the face and front and back of the chest, increased hair growth on the back, diminished carbohydrate tolerance, and the development of a "dorsal fat pad" in one patient. This combination of signs and symptoms closely resembles a mild Cushing's syndrome, which has also been observed during salicylate treatment (Cochran, Watson, and Reid, 1950). (3) The development of pericarditis immediately after arthritis had been relieved in one of the two patients who later showed signs of mild Cushing's syndrome.

All these clinical changes disappeared after γ-resorcylate had been discontinued and the attack of acute rheumatism had subsided. Glucose-tolerance tests before, during, and after γ-resorcylate in one of the patients who developed a mild Cushing's syndrome are recorded in Fig. 3.

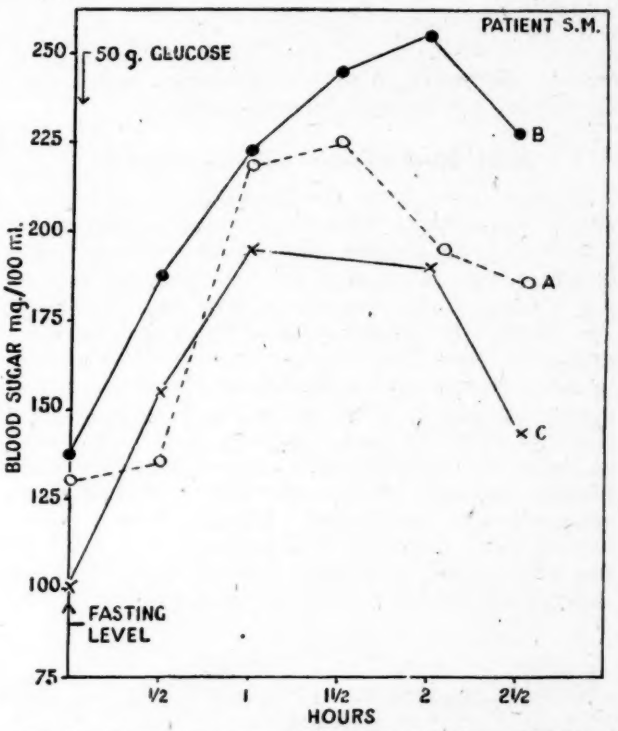


FIG. 3.—Blood-sugar curves (A) immediately before, (B) during, and (C) six days after γ-resorcylate administration in a patient who developed a mild Cushing's syndrome.

Another clinical observation of note was the absence of tinnitus and deafness in the patients treated with γ-resorcylate; in this respect it appears to differ from salicylate.

γ-Resorcylate and the E.S.R.

The changes in E.S.R. in the seven patients after administration of γ-resorcylate were compared with the results obtained in seven other patients previously treated with salicylate (7.5–10 g. daily for 9–19 days). The results are shown in Table III. The average value before

TABLE III.—*Effect of Salicylate and γ-Resorcylate on the E.S.R.*

Case	Sodium Salicylate Group E.S.R. mm./hr.			Sodium γ-Resorcylate Group E.S.R. mm./hr.		
	Immediately Before Salicylate	Peak Value During First Week	Value After 24–31 Days	Immediately Before γ-Resorcylate	Peak Value During First Week	Value After 25–32 Days
1	125	117	51 (28)	111	117	54 (27)
2	118	104	35 (31)	95	125	58 (29)
3	111	119	8 (28)	92	92	54 (29)
4	107	121	40 (24)	90	110	73 (28)
5	105	100	46 (28)	85	91	—
6	81	117	66 (24)	74	75	34 (32)
7	60	108	71 (24)	71	106	11 (25)
Average ..	101	112	45	88	102	47

The number of days from the start of treatment is shown in parentheses.

treatment was a little lower in the γ-resorcylate group, and, after an initial rise in both groups to about the same level during the first week, the average value in the γ-resorcylate group fell to 47 mm./hr. as compared with 45 mm./hr. in the salicylate group at the end of the fourth week. This difference is probably not significant, so that both drugs have about the same effect on the E.S.R.

Unusual changes in the E.S.R. were observed in two patients who were given γ-resorcylate. Within the first three days of administration of the drug the E.S.R.s of both patients fell from initial levels of 74 and 95 mm./hr. to 10 and 30 mm./hr. respectively, and then increased again to the original levels. These sudden and unexpected changes are not common in our experience, but their significance will require further investigation.

Biochemical Changes and γ-Resorcylate

Changes in water, protein, and chloride metabolism during γ-resorcylate administration were assessed by restricted fluid, nitrogen, and chloride balances. The pattern of the changes in all seven patients was more or less the same, though they differed in degree. The patient who received the largest doses of the drug showed the greatest changes. The administration of γ-resorcylate to all seven patients was quickly followed by an increase in nitrogen output in urine, which reached a peak value and then slowly returned to normal. The early changes in water and chloride balances in five of the seven patients suggested chloride and water retention which coincided with the increased nitrogen output. Later, when nitrogen output was returning to normal, a choride and water diuresis developed in all seven patients. These results are illustrated in Fig. 4, in which the early increase

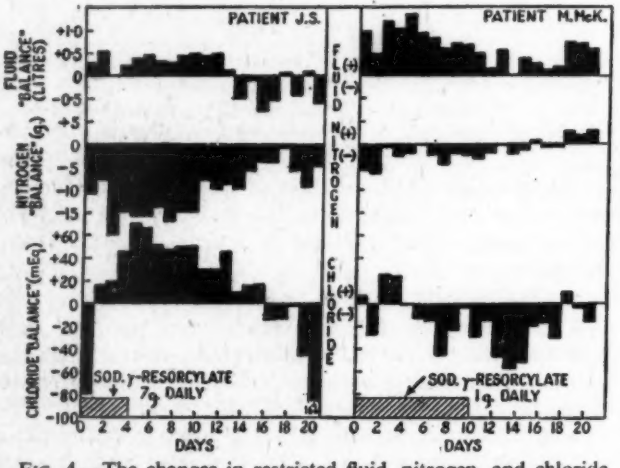


FIG. 4.—The changes in restricted fluid, nitrogen, and chloride balances following γ-resorcylate administration are shown in two patients, J. S. and M. McK., who received large and small doses respectively. The trend of the changes, particularly in nitrogen and chloride balances, was the same in both patients, but was much more pronounced in the patient who received the larger dose.

in nitrogen output and the later chloride diuresis are shown in two patients, one receiving comparatively small doses and the other large doses of the drug.

The changes in fluid, nitrogen, and chloride balances following γ-resorcylate are thus similar to those previously reported with salicylate (Reid, Watson, and Sproull, 1950).

Urinary Excretion of γ-Resorcylate

The amounts of γ-resorcylate excreted in the urine of three of the seven patients with rheumatic fever were estimated during the period of administration by the method previously described. The results, shown in Table IV, indicate that between 63% and 73% of the dose given is excreted in the urine. This amount falls within the limits excreted by healthy individuals after a single oral dose.

TABLE IV.—*Urinary Excretion of Sodium γ-Resorcylate in Rheumatic Fever*

Day	Patient M.McK. Sodium γ-Resorcylate			Patient M.J. Sodium γ-Resorcylate			Patient S.M. Sodium γ-Resorcylate		
	Dose g.	Urine mg. %	Urine mg./24hrs.	Dose g.	Urine mg. %	Urine mg./24 hrs.	Dose g.	Urine mg. %	Urine mg./24 hrs.
1	0·8	46	466	0·4	42	193	1·0	66	732
2	1·0	52	702	0·5	47	338	0·8	76	167
3	1·0	73	588	0·5	41	375	0·8	71	426
4	1·0	81	580	0·4	25	256	0·8	68	537
5	1·0	87	538	0·3	36	263	0·6	68	559
6	1·0	60	625	0·1	18	148	0·6	67	207
7	1·0	64	675	—	3	23	0·1	50	600
8	1·0	52	726	—	—	—	—	19	137
9	1·0	46	588	—	—	—	—	9	74
10	1·0	55	713	—	—	—	—	—	—
11	0·2	7	103	—	—	—	—	—	—
12	—	0	0	—	—	—	—	—	—
Total	10·0 g.		6·3 g.	2·2 g.		1·6 g.	4·7 g.		3·4 g.
	% dose excreted = 63%			% dose excreted = 73%			% dose excreted = 72%		

Summary of Results

Oral administration of comparatively small doses of γ-resorcylate to seven patients with rheumatic fever was followed by relief of acute arthritis and by a fall in temperature and pulse rate. Minor joint and muscle pains, relieved by movement, developed after the third day of dosage in five patients and a diffuse painful swelling of the fingers and hands, resembling the appearances in acromegaly, were observed in another patient. About the same time emotional instability, mental confusion, slight fever, and a dry tongue were observed in four patients. Two others developed puffiness of the face, acne-like pustules on the face, neck, and chest, increased hair growth on the back, and diminished glucose tolerance, which suggested a mild Cushing's syndrome. One of these patients developed pericarditis immediately after arthritis had been relieved. All these side-effects disappeared after γ-resorcylate was discontinued.

After a temporary rise during the first few days of γ-resorcylate administration the E.S.R. began to fall, and the main biochemical changes were an immediate increase in nitrogen excretion in the urine followed later by a chloride and water diuresis.

Discussion

The clinical effects and side-effects of γ-resorcylate in rheumatic fever, and the changes in E.S.R. and in restricted fluid, nitrogen, and chloride balances, are similar to the effects previously reported in this disease with salicylate. γ-Resorcylate in doses of about one-tenth the usual therapeutic dose of salicylate has thus about the same action as salicylate in rheumatic fever, and so far as can be judged from this preliminary trial it would appear that it is more powerful than salicylate in the sense that it induces clinical effects and side-effects for which much larger doses of salicylate are required. From the practical point of view this suggests that γ-resorcylate may have little or no advantage over salicylate in treatment of rheumatic fever, as beneficial and undesirable effects seem to be equally potentiated; but further study will be required for a final decision on this point, especially as the lethal dose of γ-resorcylate in animals is less than that of salicylate (Buttle, 1951).

The importance of the observation that γ-resorcylate is more powerful than salicylate is thus not in the practical application to treatment but in the fact that it offers an explanation of how salicylate and γ-resorcylate may

act in rheumatic fever. The evidence so far is that the isomers of salicylate, which do not chelate, have no antirheumatic action (Stockman, 1920). Salicylate, which does chelate, possesses antirheumatic properties, and γ-resorcylate, which chelates to a greater degree, is as effective as salicylate in much smaller doses. Furthermore, gentisic acid, another dihydroxybenzoic acid recently employed in treatment of rheumatic fever, is also claimed to be as effective as salicylate but less toxic in about the same dose (Meyer and Ragan, 1948; Camelin, Accoyer, Pellerat, Lafuma, and Coirault, 1949). This is consistent with the chelation hypothesis, as gentisic acid chelates to about the same degree as salicylic acid, as indicated by the similarity in their dissociation constants, which may be employed within this series of compounds as an index of chelation (Baker, 1936).

The evidence, though still not conclusive, suggests that the therapeutic action of hydroxybenzoic acids, such as salicylic, gentisic, and γ-resorcylic acids, depends on chelate ring formation. If this view finally proves to be correct, then a valuable lead for the preparation and trial of new antirheumatic compounds will have been obtained. Furthermore, since chelation is not confined to organic acids but is also shown by certain organic bases and other compounds, the variety and number of substances will be great. Finally, the hypothesis may also offer an explanation of the long-standing pharmacological puzzle of certain drugs composed of different elements having similar clinical and pharmacological actions.

Another aspect of this investigation is the general similarity in the clinical effects and side-effects of salicylate, γ-resorcylate, A.C.T.H., and cortisone. All relieve the acute manifestations of rheumatic fever and may give rise to a mild Cushing's syndrome as well as leading to the same general metabolic changes. The pharmacological investigations of Buttle (1951) and of Clayton and Prunty (1951) also indicate that in the particular tests carried out γ-resorcylate is more powerful than salicylate, and that its action resembles that of A.C.T.H. and cortisone in suppressing acute inflammatory reactions after the introduction of chemical irritants into the tissues of rats and mice and in delaying wound healing in mice.

Campbell and Wybar (1951) have also observed that it delays healing of burns in the cornea of guinea-pigs, mainly by inhibiting the formation of new fibrous tissue. The dose of γ-resorcylate required to produce these effects in animals is in the same range as that of A.C.T.H. and cortisone. This at once raises the question of how γ-resorcylate acts. The possibilities are: (1) that it acts on the anterior pituitary; (2) that it acts on the adrenal cortex; (3) that it conserves, directly or indirectly, naturally produced cortisone by preventing its destruction within the body; and (4) that it has the same action on tissues as cortisone. Clayton and Prunty (1951), using the Sayers test (Sayers, Sayers, and Woodbury, 1948), failed to observe adrenocorticotrophic activity with γ-resorcylate in hypophysectomized rats. This seems to rule out a direct action of the substance on the adrenal cortex, though the effect on the latter may be indirect through the pituitary. On the other hand, naturally produced cortisone may be conserved or both substances may have the same effect on tissues.

This last possibility is at present under investigation, and as it is probable that γ-resorcylate owes its action to chelate ring formation it is conceivable that this may also apply to cortisone. The fact that a comparatively simple substance like γ-resorcylate should have similar biological effects to the complex cortisone molecule may at first sight seem unlikely, but a precedent for this has already been established by Dodds, Golberg, Lawson, and Robinson (1939) in the similarity in action of their comparatively simple stilboestrol and the complex steroid structure of natural oestrogens. However, further discussion of the relations between salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, would serve no useful purpose until more information has been obtained on the mode of action of salicylate and γ-resorcylate and direct clinical comparison of the results of treating rheumatic fever with the drugs and hormones has been made.

Summary

The physiochemical properties of salicylate and its isomers are compared in an attempt to explain why salicylate has a therapeutic action in rheumatic fever yet its isomers have none. A notable difference is that salicylate forms an additional or chelate ring, a property not possessed by the isomers.

The possibility that the therapeutic action of salicylate may depend on chelate ring formation has been examined by investigating the antirheumatic action of γ-resorcylic acid, a dihydroxybenzoic acid which chelates to a greater degree than salicylate.

γ-Resorcylate in much smaller doses has been found to be as effective as salicylate in treatment of rheumatic fever as judged by the clinical, biochemical, and side-effects following its administration. The evidence, though still not conclusive, favours the suggestion that the therapeutic action of salicylate and γ-resorcylate is related to their common property of chelate ring formation.

The general resemblance in clinical, biochemical, and side-effects of salicylate and γ-resorcylate on the one hand, and A.C.T.H. and cortisone on the other, has been discussed with special reference to the possible mode of action of the drugs.

We thank Professor J. W. McNee for advice and criticism and for providing facilities for carrying out this work, Professor J. W. Cook for advice on the preparation of γ-resorcylate, and Dr. I. Lominski for help with preliminary toxicity tests. We are also indebted to the Department of Scientific and Industrial Research for preparing a supply of γ-resorcylate which will permit an extension of the clinical investigations.

REFERENCES

Baker, W. (1936). *Nature, Lond.*, **137**, 236.
Buttle, G. A. H. (1951). In press.
Camelin, A., Accoyer, P., Pellerat, J., Lafuma, J., and Coirault, R. (1949). *Bull. Soc. méd. Hôp. Paris*, **65**, 826.
Campbell, F. W., and Wybar, K. C. (1951). In press.
Clayton, B. E., and Prunty, F. G. T. (1951). In press.
Cochran, J. B., Watson, R. D., and Reid, J. (1950). *British Medical Journal*, **2**, 1411.
Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R. (1939). *Proc. roy. Soc. B*, **127**, 140.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
Meyer, K., and Ragan, C. (1948). *Science*, **108**, 281.
Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.
Sayers, M. A., Sayers, G., and Woodbury, L. A. (1948). *Endocrinology*, **42**, 379.
Stockman, R. (1920). *Rheumatism and Arthritis*. Edinburgh.

NOTE ON THE PHARMACOLOGY OF SODIUM γ-RESORCYLATE BY PROFESSOR G. A. H. BUTTLE

Toxicity.—The acute toxicity of the substance given by the oral route is low—5 g. per kg. is tolerated by mice. By the subcutaneous route 1 g. per kg. is tolerated whereas 2.5 g. per kg. kills all the animals. A quantity of 1 g. per kg. a day mixed with the food is well tolerated by mice for a period of three weeks, but doses of this order produce some

cloudy swelling of the tubules of the kidney; this change was not so marked, however, as with corresponding doses of salicylate.

Absorption and Excretion.—The absorption and excretion of this substance are rapid; after a subcutaneous 10-mg. dose in the rat the substance appears in the urine in one hour and is nearly all eliminated three hours after injection. After administration by mouth the quantity in the urine is smaller than after a similar dose given subcutaneously, indicating that the absorption is not so complete by the oral route.

Reduction of Formalin-induced Swellings.—If 4% formalin is injected into the pad of the foot of a mouse a swelling of the lower part of the leg results which is maximal at the end of seven days. If the animal is treated with A.C.T.H., 1 mg. equivalents twice daily, from the time of the injection this swelling is considerably reduced. Treatment with γ-resorcylate, 5 mg. daily in the diet or 0.5 mg. daily by subcutaneous injection, produced a reduction of swelling of the same order as that found with the A.C.T.H. Similar doses of sodium salicylate do not produce an appreciable effect.

APPENDIX

BY

B. E. CLAYTON,* Ph.D., M.B.

AND

F. T. G. PRUNTY, M.D., F.R.C.P.

Through the courtesy of Dr. J. Reid a sample of sodium γ-resorcylate was received.

It has been shown that A.C.T.H. causes a depletion of the adrenal ascorbic acid of hypophysectomized rats, and the test is regarded as highly specific (Sayers, Sayers, and Woodbury, 1948). We used a group of four hypophysectomized rats and an intravenous dose of γ-resorcylate in saline as high as 2.5 mg. per 100 g. rat, but no adrenocorticotrophic activity could be detected. Though unlikely, this does not rule out the possibility of γ-resorcylate acting on the pituitary gland of the intact animal. Owing to difficulties in obtaining the large number of rats required to test this, the experiment was not performed.

We described a method for consistently producing granulation tissue on the anterior abdominal wall of mice, and showed that its formation could be completely inhibited by A.C.T.H. (Clayton and Prunty, 1951). A similar effect was obtained with cortisone acetate, the dosage necessary varying with the mode of administration. Apparently γ-resorcylate under the right conditions has similar properties.

The experimental details are summarized in the Table at the foot of the preceding column.

In addition Professor Buttle has found that equivalent doses of salicylate had no effect on healing.

Thus γ-resorcylate resembles cortisone in its effect on healing. The dosages required are not very dissimilar. This may be deceiving, as γ-resorcylate is so very rapidly absorbed and excreted compared with cortisone acetate suspensions.

Dose	Mode of Administration	No. of Mice	No. of Ulcers		
			Inhibited	Impaired	Healing
Cortisone acetate					
4 mg.	Merck's suspension subcutaneously two hours before making ulcer ..	11	11	0	0
4 ,,	Merck's suspension subcutaneously, divided into two injections, six hours before and one hour after cutting	3	3	0	0
2 ,,	Merck's suspension subcutaneously six hours before cutting	3	0	3	0
2 ,,	Merck's suspension subcutaneously 17 hours before cutting	2	0	2	0
2 ,,	Suspended in propylene glycol and saline, as two intraperitoneal injections, two hours before and one hour after cutting ..	2	2	0	0
1 ,,	,, ,, ,,	2	0	0	2
Sodium γ-resorcylate					
2 mg.	Solid implanted six hours before cutting	2	0	0	2
4 ,,	,, ,, ,,	2	0	2	0
6 ,,	,, ,, ,,	2	1	0	1
4 ,,	Suspended in arachis oil, and given subcutaneously six hours before cutting	2	2	0	0
3 ,,	Aqueous solution given as a series of repeated subcutaneous injections ..	2	2	0	0
1·5 ,,	,, ,, ,,	2	0	2	0
3 ,,	Aqueous solution as two subcutaneous injections, two hours before and one hour after cutting ..	2	0	0	2
3 ,,	In propylene glycol and saline, as two subcutaneous injections, two hours before and one hour after cutting	2	0	0	2

Controls: With each experiment, controls were cut, and received cortisone diluting fluid, arachis oil, or propylene glycol and saline as necessary.

*Holden Research Fellow at St. Thomas's Hospital.

REFERENCES

Clayton, B. E., and Prunty, F. T. G. (1951). *Analyst.* In press.
Sayers, M. A., Sayers, G., and Woodbury, L. A. (1948). *Endocrinology,* **42**, 379.

TREATMENT OF SOME BULLOUS ERUPTIONS WITH AUREOMYCIN AND CHLORAMPHENICOL

BY

F. RAY BETTLEY, M.D., F.R.C.P.
Physician for Diseases of the Skin, the Middlesex Hospital

AND

E. A. FAIRBURN, M.D., M.R.C.P.
Senior Registrar, the Middlesex Hospital

Following the preliminary report of the treatment of pemphigus vulgaris with "aureomycin" (Bettley, 1950) we are now in a position to record some further experience with aureomycin and chloramphenicol in pemphigus vulgaris and certain other bullous eruptions.

The results obtained by others with similar treatment of comparable cases have shown a surprisingly variable response to this form of chemotherapy. Brainerd *et al.* (1949) treated three cases of pemphigus—one underwent a temporary remission, one was improving spontaneously at the time of treatment, while the third proved unresponsive. Spink and Yow (1949) observed no amelioration in two cases of pemphigus. Beinhauer (1950) treated seven cases of pemphigus vulgaris, all showing a uniform failure to improve. Philip (1950) recorded 19 cases: two passed into a long-standing remission, in seven there was transient improvement only, while in 10 there was no response. Combes and Canizares (1950) likewise reported only temporary remission or complete unresponsiveness in 12 patients. Barber and Yorke (1950) noted a short-lived remission in a case of pemphigus vegetans. Mathieu (1950) obtained a more favourable response, a case of pemphigus vulgaris being checked and being subsequently maintained in remission by maintenance therapy. This consisted of 2 g. of aureomycin daily, a smaller dosage being followed by relapse.

Likewise, diverse responses have been observed in the treatment of dermatitis herpetiformis. Robinson *et al.* (1949), Tzanck and Meyer (1949), Graciansky and Hardouin (1949), and Degos *et al.* (1949) recorded

favourable responses. Robinson (1950) found intravenous aureomycin therapy necessary in some instances if remission was to be achieved. Beinhauer (1950) treated five cases—two improved and three showed no change. Shaw (1950) was unable to demonstrate any improvement with this therapy.

Case 1. Pemphigus Vulgaris

This case was recorded in the preliminary report (Bettley, 1950).

The patient was a middle-aged Jewess whose illness started in July, 1949, with the appearance of sores inside the mouth, followed a month later by blisters and sores on the trunk. She was first seen on September 5, 1949, when she had many superficial erosions on the mucous membrane of the cheeks, gums, and lips, together with a few blisters on the trunk. During the next two weeks her condition deteriorated, and on September 20 she was admitted to hospital. By that time the typical clinical picture of pemphigus vulgaris was well developed and blisters covered a large portion of the body surface.

Procaine penicillin, 450,000 units twice daily for a week, was given without effect on the eruption of blisters. Suramin, 1 g. every other day, was given for a week, also without effect. The temperature at this time was around 100–102° F. (37.8–38.9° C.).

The patient's condition deteriorated rapidly and she ate very little because of the painful state of her mouth. At that time her condition was grave ; she had lost the desire to live and, indeed, seemed certain to die. From October 13 to November 25 aureomycin, 2 g. daily, was given. Within twenty-four hours of starting this treatment her general condition improved greatly. The temperature reached normal on the third day and no fresh blisters appeared after aureomycin was started. She was discharged from hospital on December 6 with the skin completely healed.

A year later she was still quite well and had had no recurrence of the pemphigus

Case 2. Pemphigus Vulgaris

A Jewess aged 47 complained of an eruption of blisters on the skin since about October, 1949. On admission to hospital on April 18, 1950, she presented an eruption of typical pemphigus vulgaris with extensive buccal ulceration. Biopsy of the skin showed acantholysis with intradermal bulla formation. Tzanck's test showed pemphigus cells.

From April 19 to May 1 chloramphenicol, 2 g. daily (loading dose 4 g.), was given without apparent effect. From May 2 to 18 aureomycin, 2 g. daily (loading dose 4 g.), was given. During this period there was considerable improvement ; the appearance of fresh bullae was very much reduced, while buccal lesions remained unaffected. The drug caused considerable nausea, and treatment had to be interrupted ; within a few days of this the eruption of bullae again increased. From May 26 to June 29 she again received aureomycin, 2 g. daily (loading dose 4 g.). The eruption was controlled, though not completely abolished. She relapsed within a few days when treatment was stopped, again because of nausea and vomiting. From July 10 to 22 aureomycin, 4 g. daily, was given. This higher dosage was administered in an attempt at complete control of the eruption instead of the partial improvement that had been obtained before. Nausea and vomiting were a serious complication, and it is doubtful what dosage of aureomycin was really absorbed. The eruption was still largely though not completely controlled, but the patient's general condition gradually deteriorated and she died on July 22. Post-mortem examination was refused.

Case 3. Pemphigus Vulgaris

This patient was an Egyptian man aged 46. In August, 1948, he had ulcers on the mucous membrane of the cheeks and tongue, followed by conjunctivitis. Blisters developed on the skin of the abdomen and axillae in January, 1949. After this his condition fluctuated but never returned to normal. In January, 1950, he was given 12 g. of aureomycin over a period of three days ; there was considerable improvement, but the treatment was not continued. He was later given stovarsol over a period of some weeks ; this gave rise to albuminuria and renal damage, which persisted. During his journey to England in September, 1950, the condition of his skin deteriorated, and when first seen on September 18 the whole surface of the body was covered with large numbers of bullae of various sizes. He was admitted to hospital the next day. The clinical appearances were those of pemphigus vulgaris. Biopsy showed intra-epidermal bullae with acantholysis. The total white blood count was 15,100, eosinophils 16%; E.S.R. 32. Fluid from a bulla contained 55% eosinophils. The patient's general condition was good and the temperature normal.

Aureomycin, 2 g. daily, was started on September 19 (loading dose 4 g.). There was at once an improvement in the condition of the skin, and the eruption of fresh bullae was almost halted. Occasional small blisters up to 0.5 cm. in diameter continued to appear, principally on the hands and feet. In the course of a fortnight's treatment all the lesions had healed with the exception of those on the hands, feet, and tongue. This state of affairs continued until October 23, when the dose of aureomycin was increased to 3 g. daily. On October 30 it was increased to 4 g. daily. Under this increased dosage the eruption of fresh lesions on the hands gradually came to an end. He was discharged from hospital on November 14 on a maintenance dosage of 1 g. daily. He later wrote to say that the condition of the hands relapsed, with the appearance of fresh blisters, on November 22 ; the dose was then increased to 4 g. daily, and the eruption disappeared in a few days. A further exacerbation occurred on December 17 and again responded within twenty-four hours to an increase in dosage to 4 g. daily.

Case 4. Pemphigus Vegetans

A man aged 56 first developed raw areas in the axillae and a sore tongue in August, 1947. After this the scalp and groins were affected. When first seen, on January 23, 1948, he showed multiple condyloma-like lesions on the inner surface of the thighs and on the scrotum. Similar lesions were present in the axillae. There was an irregular ulceration of the lower lip. The clinical appearances were those of pemphigus vegetans, and this diagnosis was confirmed by a biopsy carried out later.

The condition gradually resolved during the summer of 1948 and he was clear until October, 1949. The condition then gradually relapsed in the groins and axillae, and on February 19, 1950, he was admitted to hospital. He then showed an extensive eruption of pemphigus vegetans in the groins and axillae. A blood count showed 10,700 white cells, with 30% eosinophils ; sedimentation rate 28 (Wintrobe). The temperature fluctuated between 99 and 102° F. (37.2 and 38.9° C.).

Chloramphenicol, 2 g. daily, was started on February 22 (loading dose 4 g.). The temperature came down in step-ladder fashion and was normal after February 27. The vegetations became progressively flatter and no fresh lesions appeared. The mouth ulceration healed in a few days. By the end of March all the lesions had completely disappeared, leaving the skin of normal texture but deeply pigmented over the affected areas.

In September the patient wrote to say that his skin had remained completely well.

Case 5. Pemphigus Vegetans

An Englishman aged 69 first had a pustular eruption in December, 1949 ; this was followed by the raised granulomatous lesions of pemphigus vegetans. On admission to hospital on May 10, 1950, he had extensive vegetating erosions on the forehead and around the mouth and chin. The affected areas were studded with small deep pustules

which were sterile on culture. Tzanck's test showed pemphigus cells.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from May 11 to June 15. During this period the lesions seemed to epithelize, but they continued to extend and pustules continued to appear. From June 16 to July 5 he was given chloramphenicol, 2 g. daily (loading dose 4 g.), but no great change appeared. From July 6 to August 11 chloramphenicol was increased to 4 g. daily. Soon after beginning the higher dosage pustules ceased to appear and the lesions flattened. Eventually they disappeared completely, leaving behind normal skin with no scarring. During this period, on July 21, he developed signs of paraplegia with urinary retention, thought to be the result of a cerebral vascular lesion.

By about August 25 lesions of pemphigus vegetans had recurred on the forehead, mouth, axillae, anterior abdominal wall, perineum, fingers, and toes. Chloramphenicol, 2 g. daily (loading dose 4 g.), was given from September 18 to 24, but there was no improvement. From September 25 to December 4 he received chloramphenicol, 4 g. daily. As before, there was a satisfactory response to this higher dosage and the eruption eventually cleared completely. After December 4 the dosage of chloramphenicol was slowly reduced without recurrence. On January 16, 1951, chloramphenicol was stopped and the patient left hospital.

Case 6. Pemphigus Erythematosus

A Jewess aged 44 had had Senear–Usher syndrome since July, 1948. On admission to hospital on May 18, 1950, she showed an eruption of bullae, which progressed to form oval scaly and crusted areas towards the midline of the back and front of the trunk, and the scalp. Tzanck's test showed pemphigus cells. Biopsy showed acantholysis and intra-epidermal bulla formation.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from May 19 to June 16. All lesions gradually healed and she was discharged from hospital on June 27.

She slowly relapsed after an interval of about six weeks and was readmitted to hospital on December 27. From December 28 to January 18 chloramphenicol, 2 g. daily (loading dose 4 g.), was given. Again the eruption cleared up, and she was discharged free of lesions on January 26.

Case 7. Dermatitis Herpetiformis

An Englishman aged 70 had an erythematous eruption, with later the production of bullae, on the trunk and limbs, which started about December, 1949. Blisters became very much worse in March, 1950. On admission to hospital on April 12 there was a generalized eruption of blisters of all sizes, some arising on normal skin; erythematous patches were also present. No lesions were present in the mouth. Tzanck's test showed no pemphigus cells. A biopsy showed subepidermal vesicles with no acantholysis.

Chloramphenicol, 2 g. daily (loading dose 4 g.), was given from April 15 to May 1 and considerably improved the condition, but a few fresh bullae continued to appear. From May 2 to June 1 aureomycin, 2 g. daily (loading dose 4 g.), was given and improvement continued, but occasional bullae were still seen. Within three days of stopping aureomycin a very marked relapse followed, with the production of numerous bullae. Blisters were again controlled and almost entirely abolished with aureomycin, 2 g. daily, from June 13 to 29; then until July 17 aureomycin was given in decreasing dosage. Bullae became somewhat more frequent. Sulphapyridine, 1 g. thrice daily, and liquor arsenicalis, up to 20 min. (1.2 ml.) thrice daily, failed to prevent the occasional eruption of blisters which, at this time, were clinically typical of dermatitis herpetiformis. All active lesions had completely subsided by October 19 while under out-patient treatment with liq. hydrarg. perchlor.

When last seen (January 25, 1951) the patient was free from skin lesions.

Case 8. Dermatitis Herpetiformis

An Englishwoman aged 77 had a bullous eruption which started in June, 1950. On admission to hospital on August 4, 1950, there was a generalized eruption similar to that in Case 7. Biopsy revealed subepidermal vesicles with no acantholysis. Tzanck's test showed no pemphigus cells.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from August 4 to 15 and the blisters entirely disappeared.

Two months later vesicles typical of dermatitis herpetiformis developed on the trunk and limbs and were then controlled by the administration of liquor arsenicalis. She was well in February, 1951.

Comment

Pemphigus Vulgaris

All three of these cases presented the typical clinical appearances of pemphigus vulgaris, and in Cases 2 and 3 the diagnosis was confirmed by biopsy. In the latter we have attached importance to the presence of intra-epidermal bullae and acantholysis, indicating a lack of cohesion between cells of the Malpighian layer of the epidermis (Civatte, 1943; Rook and Whimster, 1950). The test elaborated by Tzanck (1948) depends upon the finding of detached epithelial cells showing nuclear degeneration and shrinkage of the cytoplasm in scrapings from the floor of the bullae. Such cells, according to Tzanck, are to be found only in diseases in which acantholysis is present, and the usefulness of his test has been confirmed in this country by Rook and Whimster.

In these three cases a complete or partial abolition of fresh bullae followed so quickly and strikingly after the administration of aureomycin that it was impossible not to receive the strong clinical impression that it was more than coincidence. In Case 1 the eruption was completely abolished and the patient's general condition improved at the same time. In Case 2 the severity of the eruption was repeatedly abated during aureomycin administration, relapsing twice soon after treatment was interrupted. In this case, although the eruption was largely controlled, a corresponding improvement in the patient's general condition did not take place and she appeared to die of the toxaemia and exhaustion which are usual in pemphigus vulgaris.

We must note, however, that owing to nausea and vomiting it was doubtful how much aureomycin was being retained. This complication provided a difficult problem, and we had to choose between a relapse of pemphigus and this distressing gastric upset. Perhaps parenteral administration would have met the difficulty.

In Case 3 the control of the eruption with aureomycin was again very striking, though it is evident that this patient is not cured.

The nature and cause of pemphigus vulgaris is still unknown, and the identification of a virus by Urbach and Wolfram (1936) still awaits adequate confirmation. Spontaneous remissions are a feature of the disease, and it may be that the effect of aureomycin has been only to suppress the eruption until a remission occurs. The existence of the eruption can be largely attributed to lack of cohesion between the Malpighian cells, however this may be caused; it may be that aureomycin has the effect of restoring the cohesion of these cells without necessarily attacking the cause, whether virus or otherwise. This was particularly suggested in Case 3: before treatment was started large flaccid blisters could be pressed out and made to extend themselves without

breaking. The blisters which appeared during aureomycin therapy were very much smaller, more tense, and, when pressed upon, ruptured without spreading. This observation suggests that aureomycin may restore the cohesion of the Malpighian cells without attacking the underlying cause of the disease. Such an action might be a direct effect on the Malpighian cells, or might result from an alteration of intestinal biosynthesis.

In Cases 1 and 3 aureomycin was continued over a period of many weeks. Chloramphenicol was given only in Case 2, and seemed to have no effect in the dosage employed.

Pemphigus Vegetans

In this disorder, again, spontaneous remissions often occur and response to various forms of treatment has occasionally been reported. In Case 4 chloramphenicol was started at a time when the eruption was steadily becoming worse; clinical improvement took place within a few days and the production of pustules was immediately halted. A striking feature was the fall in blood eosinophilia from 3,000 per c.mm. to *nil* in the course of two and a half weeks.

In Case 5 response to chloramphenicol was obtained only on the higher dosage of 4 g. daily; the response was then striking. When, after five weeks' treatment, the drug was stopped the condition of the skin slowly relapsed but quickly responded again when the higher dosage of chloramphenicol was resumed. In this case the blood eosinophilia remained unchanged at about 3,000 per c.mm.

Aureomycin was given in Case 5 only in the dosage of 2 g. daily; it may be that in a dosage of 4 g. daily this too would have been effective.

Pemphigus Erythematosus

This patient's eruption was mild and her general condition good. Her response to both aureomycin and chloramphenicol seems to have been favourable. It was not, however, nearly so striking as in most other cases, the improvement taking place much more gradually. We were much less convinced in this case that the patient's improvement was due to the treatment that she had received.

Dermatitis Herpetiformis

We have not used chloramphenicol or aureomycin in the treatment of dermatitis herpetiformis in its ordinary manifestations, although some favourable results have been recorded.

The two cases here were in elderly people whose eruptions resembled clinically those of pemphigus vulgaris but were distinguished by the absence of acantholysis and hence by the absence of pemphigus cells in Tzanck's test. Histologically, the bullae were subepidermal and resembled those of dermatitis herpetiformis. A diagnosis of bullous dermatitis herpetiformis was therefore made, and was supported by the development of the typical lesions of that disease later on. The bullous form of dermatitis herpetiformis may, however, lead to general exhaustion and, in these elderly patients, may well be fatal. In both cases aureomycin treatment was followed within a few days by complete or almost complete cessation of blisters and consequent improvement in the patient's condition. This bullous phase of dermatitis herpetiformis is often unresponsive to arsenic and sulphapyridine, and it seems that aureomycin has the effect of partly controlling the eruption, when it resumes the more usual features of the disease and may again be controlled with arsenic.

It is interesting to observe that in Case 8 the bullae were at first flaccid and, although they were entirely subepidermal, could be pressed out and made to extend beneath the epidermis. After the administration of aureomycin the vesicles that subsequently appeared were small and tense and could not be pressed out.

Conclusions

In this small series of cases we found that aureomycin appears to influence the production of bullae in both pemphigus vulgaris and bullous dermatitis herpetiformis. The virus aetiology of these two diseases is still unproved, and it may be that the action of aureomycin is not against an infective agent but is a direct effect on the cohesion of the cells of the epidermis.

In pemphigus vegetans, in which bullae are much less prominent, chloramphenicol appeared to be effective in melting away the vegetating masses at a surprising speed. In one of these cases, on the other hand, aureomycin seemed to be ineffective in the dosage given.

We have adopted 2 g. daily (0.25 g. three-hourly) as our standard dosage, with an initial loading dose of 4 g. In some cases, however, it seemed advantageous to give double this standard dose. Vitamin supplements were given by mouth during the period of antibiotic administration.

While response to treatment was usually obtained within a few days, we have formed the opinion that these antibiotics need to be continued for at least a month to six weeks if early relapse is to be avoided, and it seems that some of the unsuccessful trials of these drugs which have been reported may be due to dosage either too small or continued for too short a time.

None of our cases were complicated by much secondary infection. Treatment was followed by a suppression of the primary lesions of the disease, an effect which was clearly not due simply to removal of secondary sepsis.

Supplies of these drugs have not as yet been sufficient for us to determine the value of smaller maintenance doses as a means of preventing eventual relapse.

REFERENCES

Barber, H. W., and Yorke, A. (1950). *Proc. roy. Soc. Med.*, **43**, 555.

Beinhauer, L. G. (1950). *Arch. Derm. Syph., Chicago*, **62**, 290

Bettley, F. R. (1950). *Lancet*, **1**, 66.

Brainerd, H., Lennette, E. H., Meiklejohn, G., Bruyn, H. B., jun., and Clark, W. H. (1949). *J. clin. Invest.*, **28**, 992.

Civatte, A. (1943). *Ann. Derm. Syph., Paris*, 8e Sér., **3**, 1.

Combes, F. C., and Canizares, O. (1950). *Arch. Derm. Syph., Chicago*, **62**, 786.

Degos, R., Garnier, G., and Caron, J. (1949). *Bull. Soc. franç. Derm. Syph.*, **56**, 490.

Graciansky, P. de, and Hardouin, J. P. (1949). Ibid., **56**, 490.

Mathieu, P. L. (1950). *R. I. med. J.*, **33**, 24.

Philip, A. J. (1950). *Urol. cutan. Rev.*, **54**, 222.

Robinson, H. M. (1950). *Arch. Derm. Syph., Chicago*, **61**, 384.

—— Robinson, H. M., jun., and Robinson, R. C. V. (1949). *J. invest. Derm.*, **13**, 9.

Rook, A. J., and Whimster, I. W. (1950). *Brit. J. Derm. Syph.*, **62**, 443.

Shaw, C. (1950). *J. invest. Derm.*, **14**, 3.

Spink, W. W., and Yow, E. M. (1949). *J. Amer. med. Ass.*, **141**, 964.

Tzanck, A. (1948). *Ann. Derm. Syph., Paris*, 8e Sér., **8**, 205.

—— and Meyer, B. (1949). *Bull. Soc. franç. Derm. Syph.*, **56**, 431.

Urbach, E., and Wolfram, S. (1936). *Arch. Derm. Syph., Chicago*, **33**, 788.

RELIABILITY OF THE CLINICAL ASSESSMENT OF "NUTRITIONAL STATE"

BY

E. R. BRANSBY, Ph.D.

AND

W. H. HAMMOND, M.Sc.

(From the Ministry of Health)

To test how far clinicians agree in their assessment of the "nutritional state" two field trials have been made—one at Sheffield in January, 1949, and the other at Tottenham in March, 1950.* As the results of the two trials are substantially the same, the Sheffield data have, to avoid duplication, largely been omitted.

Five clinicians participated at Sheffield—namely, Drs. W. T. C. Berry, P. J. Cowin, R. B. Hawes, E. H. M. Milligan, and John Pemberton. Nine clinicians and a school nurse took part at Tottenham—namely, the above five with the exception of Dr. Milligan, together with Drs. E. W. Adcock, Cecile Asher, R. E. C. Copithorne, D. MacCarthy, Hugh S. Stannus, and Nurse Connor.† At Sheffield two clinicians, and at Tottenham four clinicians, could not participate the whole time.

201 children were examined at Sheffield and 100 at Tottenham. Of these about a quarter were "good" children and one-half "medium" children, as judged by the existing school records; the other quarter were individually chosen by the school medical officers, in association with the teachers, on account of their poor condition. Later in the report these three groups of children are referred to as "selection groups." Boys and girls aged 6 to 13 years were included.

Procedure

In both trials the children were examined by each of the participating clinicians. The order in which the children were examined was randomly arranged—that is, the "good" and "medium" children and those specially selected were mingled. The clinicians did not know beforehand how the children had been selected or the proportions of the three groups in the sample. At Sheffield 49 children and at Tottenham 24 children were, unknown to the clinicians, examined twice.

Each clinician recorded for each child (*a*) his clinical grade and (*b*) the incidence of the clinical signs listed in Table III. Certain signs were not noted at Tottenham, as the Sheffield results had shown that they had no particular association with the "nutritional" grades. It is to be noted that the clinicians had no knowledge of the medical history or the home background of the children. Neither had they access to the school medical inspection records.

All but one of the clinicians assessed what they termed "nutritional state"; the other clinician assessed "general condition." Most of the clinicians assessing "nutritional state" stated that it was doubtful if any differentiation could be made between "nutritional state" and "general condition" or "general fitness." This is the reason for putting the term "nutritional state" in inverted commas. It would prevent confusion if agreement could be reached on the terminology of such assessments. The Ministry of Education has already substituted the assessment of general condition for the assessment of nutritional state.

The trial at Sheffield was organized by Dr. H. M. Cohen, and that at Tottenham by Dr. G. H. Hogben and Dr. P. A. Tyser. We are glad to express our warm appreciation of their valued co-operation.

When used in the report the following terms have the attached definitions:

Incidence: the frequency with which a particular condition occurs.

Accordance: the agreement between the findings of different clinicians from the examination of the same children.

Reliability: the agreement between the findings of one clinician from two examinations of the same children.

Clinical Grades

Incidence (Table I).—The clinicians fall into two groups—namely, those who grade the average or normal child as "good" (Group I) and those who grade the average or normal child as "fair" (Group II). There are marked differences in each group in the number of children graded "good" (G), "fair" (F), and "poor" (P). Thus the percentage of children graded P ranged from 2 to 18 in Group I and from 14 to 35 in Group II.

TABLE I.—*Percentage of 100 Children Graded "Good" (G), "Fair" (F), and "Poor" (P), at Tottenham*

	Grade			Twofold Grouping	
	G	F	P	Satisfactory	Unsatisfactory
Group I:					
Clinician A	76	16	8	76	24
,, B	78	20	2	78	22
,, C	74	24	2	74	26
,, D	79	17	4	79	21
,, E	64	18	18	64	36
,, F	80	18	2	80	20
Group II:					
Clinician G	29	57	14	86	14
,, H	23	42	35	65	35
,, I	33	51	16	84	16
,, J	27	59	14	86	14

NOTE.—Clinician D used a fourfold grading, and grades 2 and 3 were grouped as "Fair."

In view of the differences in meaning attached to grades G, F, and P by the clinicians in Groups I and II, a certain measure of standardization between them, at least on paper, was effected by regrouping the children into two nutritional grades, "satisfactory" and "unsatisfactory." The children graded G by the Group I clinicians were regraded as "satisfactory" and the F and P children as "unsatisfactory"; the children graded G and F by the Group II clinicians were regraded as "satisfactory" and the P children as "unsatisfactory." An example will make this clear. For clinician "A," who fell into Group I, the G (76%) children were regraded as "satisfactory," the F (16%) and P (8%) children as "unsatisfactory"; for clinician "G," who fell into Group II, the G (29%) and F (57%) children were regraded as "satisfactory" and the P (14%) children as "unsatisfactory." With this regrouping the results for

*One reason for these trials was that the clinicians making the nutritional surveys for the Ministry of Health were not satisfied with the methods of assessment then being used.

†Throughout the report Nurse Connor is, for convenience, included in the term "clinician."

different clinicians were more comparable but still varied considerably. Thus, the percentage graded "unsatisfactory" ranged from 14 to 36%.

Accordance.—Table II is based on the standardized classification "satisfactory" or "unsatisfactory." The more clinicians in the trial the less the likelihood of complete agreement. Moreover, the level of agreement depends on the number of children marked down by various clinicians. These factors are taken into account by comparing the actual agreement with the agreement expected by chance. Table II shows a considerable measure of disagreement between the clinicians; agreement is better for children graded "satisfactory" than for those graded "unsatisfactory."

TABLE II.—*Accordance: Percentage Agreement Between the "Nutritional" Assessments (Standardized) at Tottenham*

	All Children		Children Graded "Satisfactory"*		Children Graded "Unsatisfactory"*	
	Actual % Agreement	% Chance Expectation	Actual % Agreement	% Chance Expectation	Actual % Agreement	% Chance Expectation
All clinicians in agreement ..	45	12	55	12	5	0
4/5 " "	74	29	83	30	40	15
2/3 " "	88	46	92	48	75	17

* The classifications "satisfactory" and "unsatisfactory" are the majority verdicts of the clinicians.

Reliability.—The children graded differently at the first and second examinations varied from 8 to 18% at Sheffield and from 4 to 37% at Tottenham for the different clinicians. These differences were on the average about half those expected purely by chance. The differences were mostly of one grade—that is, a child might be graded F on one occasion and G or P on the other—but there were occasionally differences of two grades—that is, where the child was graded G on one occasion and P on the other. The clinicians who down-graded the most children had the most discrepancies, simply because they had a greater possibility of variation than had those clinicians who down-graded fewer.

Clinical Signs

Incidence (Table III).—There are wide variations in the incidence of the different signs as recorded by the several clinicians.

Accordance (Table III).—There was much disagreement between clinicians. This was more marked where the sign was present than where it was absent.

Reliability.—The level of reliability depends to some extent on the level of incidence. For example, if a clinician does not record a particular sign as present in any child there must of necessity be good agreement between the first and second examinations. The actual agreement at the two examinations, compared with the agreement expected by chance, is shown in Table III. On the average the actual agreement is somewhat more than is expected by chance. For some signs—for example, lethargy and poor muscle tone—there was considerable disagreement. On the whole the reliability was not particularly good.

An interesting feature of the results is that the reliability of the nurse and her agreement with the doctors was as good as that of the individual doctors.

Relationship between Clinical Grades and Clinical Signs

Table III also shows the incidence of the clinical signs for the nutritional grades G, F, and P at Tottenham. Both at Sheffield and at Tottenham the incidence of the following signs increased as the nutritional grade worsened: pallor, fatigue rings, mucous membrane pallor, lethargy, poor posture, diminished fat, poor muscle tone, poor muscle development, poor grip, inelastic skin. At Sheffield the incidence of folliculosis, gingivitis, and enlarged tongue papillae varied little according to nutritional grade. Table IV shows that each clinician recorded least clinical signs in his G grade, more in F, and most in P.

There was a high degree of association between the incidence of clinical signs and "nutritional" grade. This was so for all participating clinicians, though some put more emphasis on particular signs. Thus there was for all clinicians a close association between "nutritional" grade and muscular development, while the association with "inelastic skin" was close for only four clinicians. The Group I clinicians tended to down-grade children with fewer clinical signs than did the Group II clinicians. For example, a child with a certain number of signs might be graded P by Group I, but F by Group II. Even with the standardized (satisfactory/unsatisfactory) grading, there is still much variation in the incidence of clinical signs in the two grades as recorded by different clinicians.

TABLE III.—*Clinical Signs as Recorded by the 10 Clinicians at Tottenham*

	Pallor	Fatigue Rings	Mucous Membrane Pallor	Lethargy	Poor Posture	Diminished Fat	Poor Muscle Tone	Poor Muscle Development	Poor Grip	Inelastic Skin
Incidence: range (%)	2–34	15–38	0–8	0–20	21–35	7–42	0–31	3–43	4–24	0–14
Accordance (%):										
Sign absent:										
All clinicians in agreement ..	53	22	79	65	27	59	43	56	56	78
4/5 or more in agreement ..	85	71	99	94	79	79	85	78	91	96
Sign present:*										
All clinicians in agreement ..	0	0	4	0	15	0	0	0	0	0
4/5 or more in agreement ..	23	35	0	0	55	47	0	14	0	0
Reliability:										
Mean % agreement	80	79	97	85	72	81	85	78	90	
Range %	58–100	54–83	75–100	71–100	58–88	71–92	71–96	67–83	75–100	
% agreement expected by chance	58	49	94	80	54	68	75	64	84	
% incidence of clinical signs for grades G, F, and P:										
Group I clinicians:										
Grade G	12	20	1	4	16	4	7	3	4	3
" F	43	54	16	18	57	61	37	57	26	6
" P	57	69	25	27	74	78	45	71	27	16
Group II clinicians:										
Grade G	6	13	0	5	14	0	2	0	3	0
" F	10	32	2	7	21	13	5	4	7	9
" P	28	54	3	21	72	48	34	42	20	27

* Whether the sign was present or absent was determined by the majority verdict of the clinicians.

TABLE IV.—*Clinical Signs Per Child According to "Nutritional" Grade*

	Grade G	Grade F	Grade P	
Group I:				
Clinician A ..	1·0	3·8	4·1	
" B ..	0·5	2·9	3·0	
" C ..	0·6	2·8	5·5	
" D ..	0·5	3·9	5·4	6·3*
" E ..	0·5	3·4	4·9	
" F ..	1·2	3·0	4·0	
Mean ..	0·7	3·5	4·5	
Group II:				
Clinician G ..	0·4	0·7	2·8	
" H ..	1·0	1·5	4·3	
" I ..	0·2	0·9	1·8	
" J ..	0·1	1·2	5·0	
Mean ..	0·4	1·1	3·5	

* This clinician used four grades.

Relationship between Nutritional Grades and Original Selection Groups

As has already been described, the Tottenham children fell into three groups; those who were "good" as judged by existing school records, those who were "medium" as judged by their existing school records, and those selected on grounds of poor nutrition. These are now termed "selection groups" and called groups "A," "B," and "C" respectively. At Tottenham the clinicians graded G a high proportion of the A children, fewer of the B children, and least of the C children (Table V). In considering these results it must be noted that special efforts were made to obtain really poor children for the C group. The Group I and II clinicians behaved somewhat differently in their gradings of the selection groups. The Group I clinicians show little difference between the A and B children, but make a sharp distinction between B and C; while the Group II clinicians differentiate more uniformly between the three groups.

TABLE V.—*"Nutritional" Grade According to Original Selection Group at Tottenham*

"Nutritional" Grade:	Group A			Group B			Group C		
	G	F	P	G	F	P	G	F	P
Group I: Average for all clinicians	92	7	1	81	18	1	45	40	15
Range ..	84–100	0–15	0–8	66–87	13–34	0–5	20–58	22–71	6–44
Group II: Average for all clinicians	65	29	6	29	62	9	4	46	50
Range ..	54–84	16–43	0–12	24–32	57–66	3–18	0–6	24–68	27–76

The number of clinical signs per child recorded by each clinician increased from the A to the B children and still further to the C children (Table VI).

TABLE VI.—*Number of Clinical Signs Per Child According to Selection Group at Tottenham*

	Group A	Group B	Group C
Clinician A ..	0·9	1·5	2·5
" B ..	0·4	0·9	1·0
" C ..	0·4	0·8	1·7
" D ..	0·7	0·8	2·6
" E ..	0·4	0·7	1·5
" F ..	0·9	1·6	4·1
" G ..	0·5	0·8	2·1
" H ..	0·9	1·7	2·8
" I ..	1·5	2·1	2·9
" J ..	0·9	1·4	3·0

Consistency of the Grading of Groups of Children

Table VII shows the percentage of children graded "satisfactory" at Sheffield and Tottenham by four clinicians who participated in both trials. The four agree that Tottenham was a worse group than Sheffield. Moreover, their standards in relation to each other are the same in both trials, made at about a year's interval. Comparison between clinicians can also be made for selection groups A, B, and C, both at Tottenham and at Sheffield (Table VII). The clinicians record fairly small but consistent differences between groups A and B and fairly large differences between groups B and C. This suggests that not only do they distinguish between groups but they also agree fairly well on the size of the differences. It must be noted that this analysis applies to the standardized (satisfactory/unsatisfactory) grading and not to the original gradings (G, F, and P) used by the clinicians.

TABLE VII.—*Percentage of Children Graded "Satisfactory" in the Various Selection Groups at Sheffield and Tottenham*

	% of all Children Graded Satisfactory		% of Children Graded Satisfactory in the Three Selection Groups					
	Sheffield	Tottenham	Sheffield Selection Group			Tottenham Selection Group		
			A	B	C	A	B	C
Clinician A						92	87	53
" B	84	78	100	91	63	96	84	58
" C	84	74	98	88	60	96	87	44
" D						92	89	54
" E	79	65	100	87	53	83	82	58
" F						100	87	56
" G						96	87	44
" H	79	64	94	80	44	93	82	24
" I						100	89	69
" J						88	97	72
" K						—	—	—

Discussion

The clinical assessment of nutrition has two main purposes—the assessment of the individual and the comparison of population groups. For the former, reliability and accordance are paramount; for the latter, individual discrepancies may even out to obtain a correct overall picture. For the individual, the present results confirm those of Huws Jones (1938) in this country, and of Franzen (1929) and Bean (1948) in America—namely, that the clinical assessment is unreliable. Bean (1948) concludes: "The clinical assessment of nutrition is of great complexity. Not only is the interpretation of signs and symptoms a matter for dispute but physicians trained in the discipline of nutrition vary significantly in what they actually see in examining a person."

In relation to the nutrition of population groups, two positive results emerge from the trials. Although clinicians adopt different standards for their nutritional grades, it seems that they maintain these standards relative to one another and can thus distinguish between groups of children and agree on the order of differences. This appears to be so even for examinations made at an interval of more than a year. This does not necessarily mean that clinicians maintain their standards over such a period, but that they maintain their standards relative to one another. Nor does it mean that the findings of different clinicians examining different groups of children are directly comparable.

The second positive result is the relationship between nutritional grades and clinical signs. The present result confirms those already reported by Adcock, Hammond, and Magee (1947)—namely, that there was a high degree of association between certain clinical signs and nutritional grades. The present trials go further and show that clinicians of widely different experience seem to agree substantially on the importance and relevance in relation to nutritional assessment of certain signs which have been called "grading criteria." This suggests that these grading criteria could either be used as separate faetors (especially if they could be made more objective) or could be combined into a general grading according to some system of weighting. This opens up the possibility of distinguishing between degrees of severity of signs and whether the signs occur singly or in combination with others.

It must, however, be recognized that it may be as difficult to obtain standardization or objectivity for the clinical signs as for the nutritional assessment. Such an aggregate result based on signs need not, of course, be termed a nutritional assessment. In any case it seems doubtful whether it is possible, under present conditions in this country, to differentiate between nutritional assessment and an assessment of general condition or fitness. It must be emphasized that from the very nature of the clinical method perfection cannot be expected. An attempt should be made to assess its good and bad points against possible alternatives and to decide how the method can best be used and what modifications should be made.

Summary

Two trials were made to test the reliability of the clinical assessment of "nutritional state," the first at Sheffield in January, 1949, the second at Tottenham in March, 1950. Five clinicians took part at Sheffield and nine clinicians and a school nurse at Tottenham.

For each child "nutritional state" was taken to include assessments of "general condition" and the incidence of certain clinical signs.

Both for the clinical grades and for the clinical signs there was a considerable lack of agreement between clinicians in their findings for individual children and for the group of children as a whole. A number of children were examined twice, and there was, for the same clinician, considerable disagreement in the findings of the two examinations.

There was a high degree of association between clinical grade and the incidence of certain clinical signs.

Comparison of the clinical assessments made by those clinicians who took part in both trials and the assessments by the different clinicians of different groups of children at Tottenham shows that the clinicians maintained their standards relative to one another and that they could distinguish between groups and generally agree on the order of the differences.

The high degree of association between nutritional grades and the incidence of certain clinical signs suggest that if the latter could be made more objective they could be used separately for grading purposes or could be combined into a general grading according to some system of weighting.

The trials at Sheffield and Tottenham were entirely dependent on the participation of the clinicians and the school nurse. We are especially glad to acknowledge our indebtedness to them and to express our thanks. We wish to make it clear, however, that this paper represents our interpretation of the data and that only our personal views are expressed. This does not imply that those participating in the trials agree with the interpretation of the data or with the views expressed. We wish to record again our appreciation of the valued co-operation of Dr. H. M. Cohen, at Sheffield, and Dr. G. H. Hogben and Dr. P. A. Tyser, at Tottenham. We are also glad to thank Dr. H. E. Magee for his interest and advice.

REFERENCES

Adcock, E. W., Hammond, W. H., and Magee, H. E. (1947). *J. Hyg., Camb.*, **45**, 65.
Bean, W. B. (1948). *J. appl. Physiol.*, **1**, 458.
Franzen, R. (1929). *Physical Measurements of Growth and Nutrition*. Amer. Child Hlth Ass., New York.
Jones, R. H. (1938). *J. R. statist. Soc.*, **101**, 1.

THE PERIPHERAL CIRCULATION DURING GENERAL ANAESTHESIA AND SURGERY

BY

R. B. LYNN, M.D., F.R.C.S.

AND

RALPH SHACKMAN, M.B., B.S., F.R.C.S.

(From the Department of Surgery, Postgraduate Medical School of London)

Changes produced in the peripheral circulation by general anaesthesia may be evident in the flushed warm skin which develops soon after induction, and may be recorded by finger plethysmography (Foster *et al.*, 1945). We have used calf, foot, and hand plethysmographs to measure the circulatory changes which occur when cyclopropane, ether, "trilene," nitrous oxide, oxygen, thiopentone, and gallamine triethiodide ("flaxedil") are used in varying combinations (Tables I and II), and have shown that further readjustment of the circulation develops later during lengthy major operations. The state of the limb circulation can be a considerable aid to the assessment of the general circulatory state of a patient undergoing major surgery under general anaesthesia.

Method of Study

The plethysmographs (Barcroft and Edholm, 1943) were constructed of "perspex" and contained built-in thermostatically controlled heating units. Displacement of water (kept at $32° \pm 1°$ C. for the hand and foot, and at $34° \pm 1°$ C. for the calf) was used to measure the limb flows. Snugly fitting diaphragms were bolted to the plethysmograph, and the cuffs, made of thin rubber sheeting, were sealed to the skin with rubber cement. Several turns of self-adhering rubber tape were wound around the cuffs as reinforcement, with care to avoid venous congestion. Thick rubber pressure tubing connected the plethysmograph to a float recorder writing on a mobile bench kymograph.

When calf flows were measured egress of blood from the foot into the calf was interrupted by inflation of an occluding cuff at the ankle above systolic pressure (Barcroft and Edholm, 1943).

Limbs flows were measured, first in the pre-anaesthetic sedated period before the induction of anaesthesia, and then throughout the operative procedure (pre-operative sedation was by morphine, atropine, and hyoscine in varying combinations). Several readings were taken during every five-minute period, and the average value was used as the index of limb flow. The blood pressure and pulse rate were recorded at regular periods throughout the studies.

TABLE I.—*Group I: Minor Operations*

Case No.	Age and Sex	Operation	Anaesthetic	Part Studied	ml./100 ml./minute		
					Resting Flows	Peak Flows	Final Flows
1	19 F	Excision thyroglossal cyst	Thiopentone, N_2O, O_2, trilene	Calf	2·8	7·0	6·0
2	59 M	Cystoscopy and herniotomy	Thiopentone, cyclo., O_2	,,	2·2	7·4	6·0
3	42 M	Herniorrhaphy	,, ,, ,,	,,	1·5	9·5	8·0
4	50 F	Amputation of arm	N_2O, O_2, cyclo.	,,	2·5	6·2	6·0
				Average	2·3	7·5	6·5
5	57 F	Herniorrhaphy	Thiopentone, N_2O, O_2, ether	Foot	1·0	6·5	4·0
6	40 M	Herniotomy	Thiopentone, N_2O, O_2, trilene	,,	2·4	19·0	18·0
7	34 F	,,	Thiopentone, N_2O, O_2	,,	1·4	9·8	10·0
8	27 M	,,	Thiopentone, N_2O, O_2, flaxedil	,,	2·1	30·0	27·0
				Average	1·7	16·3	14·8
9	39 M	Herniorrhaphy	Thiopentone, N_2O, O_2	Hand	4·6	14·0	8·0
10	34 F	Excision thyroglossal cyst	Thiopentone, O_2, ether, trilene	,,	1·4	12·3	11·3
11	36 F	Herniotomy	Thiopentone, N_2O, O_2	,,	2·2	11·0	10·8
12	69 F	Herniorrhaphy and orchidectomy	Thiopentone, cyclo., O_2	,,	11·0	21·5	13·0
				Average	4·8	14·7	10·8

Blood flows were measured in the calf, foot, and hand. Forearm flows were not measured, as it has been generally agreed (Abramson, 1944) that calf and forearm flows are comparable and that both are an index of muscle circulation.

Two groups of patients were studied. Group I included patients undergoing short and relatively minor operations, and Group II those undergoing lengthy major operations. Hand flows were not measured in Group II, because it was found that the presence of a hand plethysmograph on a patient embarrassed the surgeon during a lengthy abdominal operation. We have accepted that hand and foot flows are comparable, and that both are an index of circulation in the skin (Abramson, 1944).

Results

Group I: Short and Minor Operations (Table I).—The pre-anaesthetic limb flows averaged 2.3 ml. per 100 ml. in the calf, 1.7 ml. in the foot, and 4.8 ml. in the hand. An increase in limb flow began immediately after the induction of anaesthesia, but the maximum increase in flow often did not develop until 15 to 30 minutes had elapsed (Figs. 1, 2, and 3). The average peak flows during operation were 7.5 ml. per 100 ml. in the calf, 16.3 ml. in the foot, and 14.7 ml. in the hand. In 11 of the 12 patients in this group the marked increases in limb flow persisted throughout the duration of the operations; even the single exception (Case 12) had a final flow which was 20% greater than the pre-anaesthetic resting level.

Group II: Lengthy Major Operations (Table II).—The pre-anaesthetic limb flows averaged 2.4 ml. per 100 ml. in the calf and 2.3 ml. in the foot. The average peak flows during operation were 7.8 ml. per 100 ml. in the calf and 9.2 ml. in the foot. These increased flows were not maintained as the operation progressed, and the final flows in this group averaged 2.3 ml. per 100 ml. in the calf and 2 ml. in the foot (Figs. 4 and 5).

Discussion

(For the purpose of the discussion of the significance of the changes in limb flow and blood pressure the values of the changes are expressed as percentages of the corresponding primary resting levels. For example,

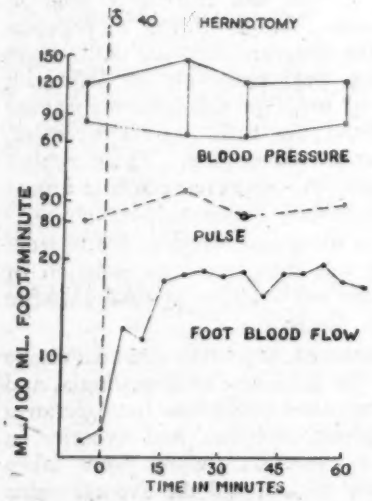


FIG. 1.

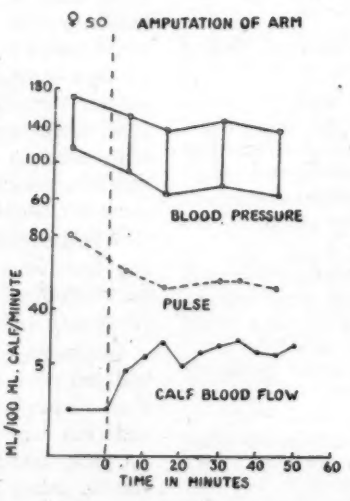


FIG. 2.

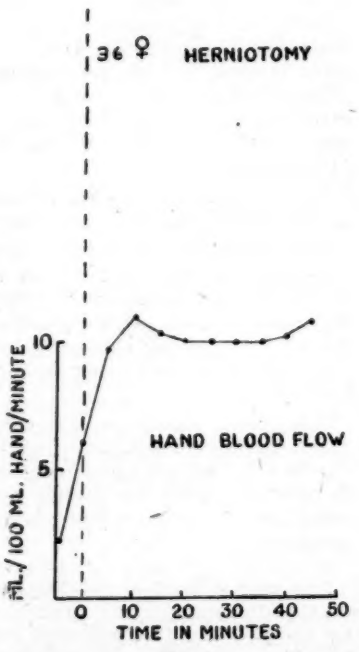


FIG. 3.

FIGS. 1, 2, and 3 (Minor Operations).—Zero time indicates induction of anaesthesia. The pre-anaesthetic readings are averages taken over periods of time varying from 10 to 30 minutes. The limb flows are maintained during operation.

TABLE II.—*Group II: Major Operations*

Case No.	Age and Sex	Operation	Anaesthetic	Part Studied	ml./100 ml./minute		
					Resting Flows	Peak Flows	Final Flows
1	50 M	Gastrectomy	Thiopentone, cyclo., O_2, flaxedil	Calf	1·0	3·0	1·0
2	72 F	Colectomy	Thiopentone, O_2, cyclo., flaxedil	,,	6·0	15·0	8·0
3	62 M	Gastrectomy	Thiopentone, cyclo., O_2, flaxedil	,,	2·5	15·0	2·0
4	64 F	,,	Thiopentone, cyclo., O_2	,,	1·5	5·9	1·0
5	35 F	,,	Thiopentone, N_2O, O_2, flaxedil	,,	1·4	5·3	2·0
6	44 M	Laparotomy	,, ,, ,, ,,	,,	3·5	8·0	2·0
7	43 M	Closure of vesico-perineal fistula	Thiopentone, cyclo., O_2	,,	1·7	5·0	2·0
8	47 M	Gastrectomy	Thiopentone, cyclo., O_2, flaxedil	,,	1·2	5·2	0·6
				Average	2·4	7·8	2·3
9	68 F	Gastrectomy	Thiopentone, cyclo., O_2, flaxedil	Foot	1·3	2·5	0·7
10	70 F	,,	,, ,, ,, ,,	,,	2·2	8·5	2·0
11	80 F	,,	,, ,, ,, ,,	,,	2·0	5·0	1·0
12	46 M	,,	,, ,, ,, ,,	,,	2·8	13·3	4·9
13	52 M	,,	,, ,, ,, ,,	,,	2·5	13·0	2·0
14	38 M	,,	,, ,, ,, ,,	,,	2·0	12·5	1·5
15	36 F	Exploration of gall-bladder and common bile duct	,, ,, ,, ,,	,,	3·0	9·5	2·0
				Average	2·3	9·2	2·0

if a limb flow increases from a resting basal level of 2 to a peak of 8 and subsequently decreases to the original level of 2, the increase from the basal level to the peak flow is recorded as 300%, while the subsequent fall is also 300%. Similarly, if a primary mean arterial pressure of 100 increases to 120 in the period of the peak flow and subsequently declines to 80, the increase is recorded as 20%, while the subsequent decrease is 40%.)

It has been confirmed by venous occlusion plethysmography that the peripheral circulation undergoes profound changes during general anaesthesia and surgical operations. Increased limb flows are maintained during the whole period of relatively minor operations and during the earlier phases of more prolonged and severe operations. During the later phases of more prolonged and severe operations the limb flows decline in most cases and become equal to or somewhat less than the pre-anaesthetic resting levels.

An increased limb flow might represent a passive response to an increase of blood pressure, without change in calibre of the vessels in the limb concerned, or could result from active vasodilatation in the limb vessels. But consideration of the simplified version of Poiseuille's formula R= (where R=resistance, P= mean blood pressure, and F=flow) makes it clear that enormous increases of blood pressure would be needed to produce the large increases in limb flow that we have noted and which averaged the equivalent of 360% of the average pre-anaesthetic resting flow. As the maximum increase in mean blood pressure that we have noted in any single patient was only 33% above the corresponding pre-anaesthetic resting pressure, and in fact, as can be seen in Figs. 1, 2, 4, and 5, the blood pressure usually remained virtually unaltered from the pre-anaesthetic level, it is concluded that the increase in peripheral blood flow noted during anaesthesia results from active vasodilatation in the limb vessels.

The decrease in limb flow from the peak level, noted in the later stages of the more severe operations, could be due to a fall in blood pressure or to relative vasoconstriction in the limb vessels. But the average decrease in flow from the peak of vasodilatation was equivalent to 270% of the average pre-anaesthetic flow, while the corresponding average fall in mean arterial pressure was equivalent only to 19% of the average pre-anaesthetic pressure. Therefore it is unlikely that alteration in

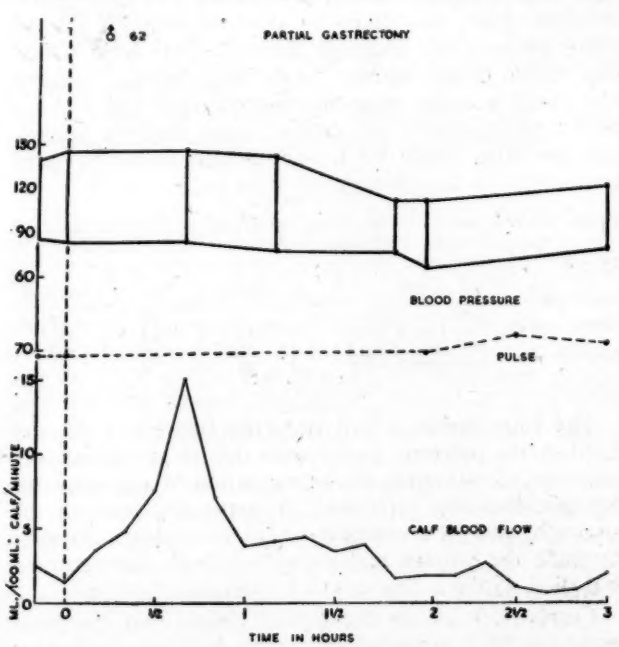


FIG. 4.

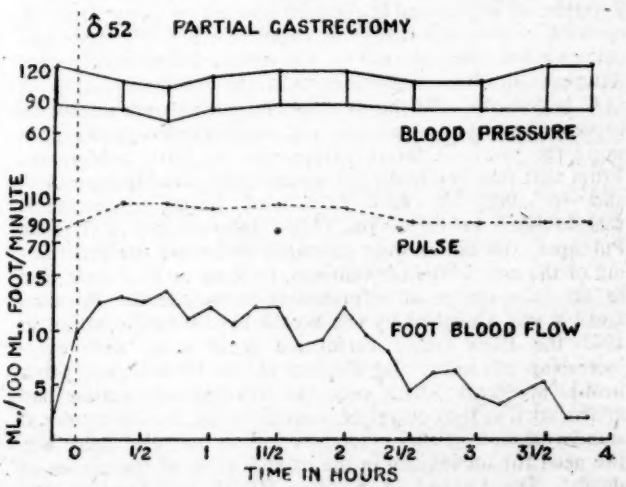


FIG. 5.

FIGS. 4 and 5 (Major Operations).—The increased limb flows are not maintained during the later phases of the operation.

mean arterial pressure alone could account for the large decrease in limb flow, and it is concluded that the change is due to a relative vasoconstriction in the peripheral circulation.

The rapid onset of vasodilatation after induction of anaesthesia suggests that the primary alteration in calibre of the peripheral vessels is an expression of release of normal vasomotor tone, and is due to the action of the anaesthetic agent on the vasomotor centre. But the vasodilatation could also be due to a direct action of the anaesthetic agent on the walls of the blood vessels (Cushny, 1928). The large distribution of vasomotor nerves to the skin, and the great number of arteriovenous anastomoses in the foot and hand (Lewis, 1936) could both equally well account for the relatively greater flows which develop in these regions.

The development of relative vasoconstriction in the later stages of the major operations probably expresses a circulatory readjustment for maintenance of the blood pressure. It occurs despite the fact that the amount of anaesthetic used increases in proportion to the length of the operation.

There is a limit to the duration and degree of vasoconstriction that can occur during lengthy major operations. This limit has not been determined, and may indeed vary from patient to patient. But it can be inferred that intense and prolonged vasoconstriction is indicative of maximal compensation and presages overt clinical shock.

We are grateful to Professor Henry Barcroft, of the Department of Physiology, St. Thomas's Hospital, for guidance.

REFERENCES

Abramson, D. I. (1944). *Vascular Responses in the Extremities of Man in Health and Disease.* University of Chicago Press, Chicago.
Barcroft, H., and Edholm, O. G. (1943). *J. Physiol.*, **102**, 5.
Cushny, A. R. (1928). *Textbook of Pharmacology and Therapeutics*, 9th ed. Churchill, London.
Foster, A. D., jun., Neumann, C., and Rovenstine, E. A. (1945). *Anesthesiology*, **6**, 246.
Lewis, T. (1936). *Vascular Disorders of the Limbs.* McMillan, London.

A hundred years ago last month the first conference on international health problems was held in Paris, when the representatives of 12 nations met to discuss quarantines and lazarettos in the Mediterranean. After six months' work the first International Sanitary Convention was signed. The Republic of Venice had introduced quarantine in the fifteenth century, and every maritime country eventually followed suit; but the systems used by the various governments were different and often conflicting. Also the cholera epidemic of 1832 had shown that the quarantine systems were unable to prevent the spread of disease and badly needed re-examination; the result of this situation was the Paris conference. From that time international co-operation steadily increased, and in 1907 the first permanent health organization was founded in Paris—the Office International d'Hygiéne Publique. Its duties were primarily to ensure the functioning of the quarantine conventions, to draw up new ones, and to act as a centre of information on pestilential diseases. Until it was absorbed by the World Health Organization in 1947 the Paris Office performed these tasks with ever-increasing efficiency. By the end of the 1914–18 war other health problems which required international action had arisen, such as the control of narcotic drugs, the international standardization of sera, vaccines, and so on; also there was the need for uniformity in the classification of the causes of death. The League of Nations Health Organization, the predecessor of W.H.O., was established in 1921. (A fuller account appeared in *The Times* of July 23.)

THE FAMILY DOCTOR AND DIABETIC COMA

BY

J. C. PEASE, D.M., M.R.C.P.
Senior Registrar, Radcliffe Infirmary, Oxford

AND

A. M. COOKE, D.M., F.R.C.P.
Physician, Radcliffe Infirmary, Oxford

Diabetic coma most frequently develops outside hospital, therefore we feel it important to draw attention to some of the ways in which the patient and his family doctor can prevent the onset of coma.

Since 1922 there has been a fall in the incidence of diabetic coma (Joslin, 1946). The reasons for this decline are the introduction of insulin therapy, the use of sulphonamide and antibiotic drugs, the increasing number of diabetic clinics—the last resulting in better control of both patient and disease—and a greater understanding of the disease by patient and doctor.

The mortality of diabetic ketosis has fallen because diabetic precoma is treated more effectively, with the result that fewer cases progress to coma, and also because the management of diabetic coma is improving each year. The chief factors responsible are the larger doses of soluble insulin given in the early stages of the illness, the more liberal use of intravenous fluids—a form of therapy revolutionized by the introduction of the "drip" method of transfusion (Marriott and Kekwick, 1935)—a clearer understanding of the type of fluids which should be given, the realization of the importance of gastric lavage, and the control of infections by sulphonamides and antibiotics. In spite of all these advances in treatment diabetic coma still occurs and all too often results in death.

The figures given in Table I illustrate the difference in prognosis between precoma and coma. The cases have been divided into two periods, each of nine years. October, 1941, was taken as the mid-point of the 18 years because the Radcliffe Infirmary Diabetic Clinic was started in that month. In defining diabetic precoma and coma we have used the former expression when a patient is conscious but drowsy from diabetic ketosis, and the latter when he is unconscious from the same cause.

TABLE I.—*Outcome of 111 Cases of Precoma and 74 Cases of Coma, 1932–50*

	Year	Alive	Dead	Survival
Coma	1932–1941 (Sept.)	2	34	6%
	1941 (Oct.)–1950	15	23	39%
Precoma	1932–1941 (Sept.)	22	5	81%
	1941 (Oct.)–1950	80	4	95%

The four deaths which occurred between 1941 and 1950 in the precoma group were due to (1) pulmonary embolus, (2) toxaemia after amputation of a gangrenous leg (an anaerobic infection), (3) acute dilatation of the stomach, and (4) a cerebral vascular accident. In each instance the patient had recovered from the precoma but died within a few days of admission.

Comparison of the two periods shows that the prognosis for both precoma and coma has improved since 1941, but that the death rate for diabetic coma is still very high.

Illustrative Cases

The following four cases illustrate some of the common faults in dealing with ill diabetic patients.

Case 1.—A 36-year-old woman in whom diabetes had been diagnosed six years ago. At the time of her illness she was 18 weeks pregnant. Three days before admission she developed acute pyelonephritis, and on the following day was vomiting. She took insulin on the morning of the day before admission, but not afterwards, and by the evening was drowsy. At 2 a.m. next day her doctor gave her a sedative because she was restless; by 7 a.m. she was unconscious. She arrived in hospital four hours later.

Comment.—The doctor was called in too late, the insulin dosage was reduced instead of being increased, and there was great delay in sending the patient to hospital.

Case 2.—A 63-year-old woman known to have had diabetes for years. Five days before admission she developed cough, headache, and vomiting. She had had no insulin until admitted to a cottage hospital on the fourth day of the illness: then she was given 20 units of soluble insulin, 20 units of zinc-protamine insulin, and ½ oz. (14 g.) of glucose in water to drink. She received a further 20 units of insulin on the following morning; she did not reach the Radcliffe Infirmary until 12.30 p.m.

Comment.—The patient was given an inadequate dose of insulin and would have been better sent to the Radcliffe Infirmary direct instead of being admitted to the local hospital.

Case 3.—A man aged 69 not known to have diabetes. He was seen by his doctor five days before admission to hospital, when he gave a history of one month's loss of weight, lassitude, and thirst. Three days later the patient was drowsy and dehydrated, and his urine contained a large amount of sugar. He was admitted to hospital two days later, at 4.45 p.m.

Comment.—The delay in diagnosis and initiation of treatment proved fatal to the patient.

Case 4.—A girl aged 19. Diabetes had been diagnosed in 1940, four years before her death. Eighteen months before death she gave up her diabetic diet, and twelve months later stopped taking insulin. The symptoms and signs of uncontrolled diabetes returned. On the day before coming into hospital she became feverish and began to vomit. That evening she was warned by her doctor to "take care" because she was a diabetic. No insulin was given. Next morning she was admitted to hospital in deep coma with signs of peripheral circulatory failure.

Comment.—Insulin should have been given immediately and the patient sent to hospital that night.

Education of the Patient

The amount which a patient is able to learn varies according to his individual capacity, but almost every diabetic is capable of learning a few fundamental facts—a matter of great importance, since the education received in the management of his diabetes should act as his first line of defence against the onset of diabetic ketosis. The patient should know amongst other things that: (1) one of the essentials in treatment is to take enough insulin to keep glycosuria and ketonuria under control; (2) infections make diabetes worse; (3) urine testing is more than ever important during illness; (4) if a full diet is not acceptable, at least the carbohydrate of the diet should be eaten; and (5) if vomiting is persistent half the normal dose of insulin should be taken as a "first-aid" measure and a doctor summoned immediately.

At the Radcliffe Infirmary Diabetic Clinic patients are given some instruction at their first visit and also receive a copy of a pamphlet in which are set out clearly and simply the main facts about diabetes. This dual method of instruction is used because many patients are unable to recall the spoken word by the time they reach home, because another member of the family may, after reading the pamphlet, be able to help the patient, and because in a busy out-patient department there is not time to give each patient a comprehensive dissertation on diabetes. At subsequent visits the patients are encouraged to ask questions, and any part of the book which has not been understood is explained. There is a section describing what to do if ill, and another section dealing very simply with the symptoms and signs of diabetic coma; the patients are urged at the first sign of trouble to call in a doctor at once. Patients with a low intelligence are made to understand at least that if they are unwell a doctor should be consulted straight away.

Bruch (1949) has shown that the education of the diabetic child and his parents is also of great importance, as often the doctor can improve the child's diabetes by helping the parents to adopt a more reasonable attitude towards the child's disease.

The Family Doctor's Part

The doctor's part in dealing with ill diabetic patients is described in textbooks of medicine and medical treatment, and recently in two informative articles by Oakley (1949). Analysis of the 23 fatal cases of coma occurring at the Radcliffe Infirmary between 1941 and 1950 has served to emphasize the following facts.

Infection was the precipitating factor in 19 instances. Lowered carbohydrate tolerance occurs in infection, and unless treatment is adequate ketosis develops. This may lead to or be accompanied by anorexia or vomiting, which will increase the state of dehydration already induced by the fever and polyuria. If this train of events is not checked precoma will develop, followed in its turn, after a period of days or even hours, by coma. If the doctor is unable to check the development of ketosis he should immediately send the patient to the nearest hospital capable of dealing with such an emergency.

Delay.—Joslin (1950) quotes Root as saying that the lowness of the death rate among those of his patients who were admitted in diabetic coma was to a large extent because the family doctor had given insulin before the patient was placed in the ambulance. In the 23 present cases only four received insulin before coming into hospital (see Table II). In at least eight instances, from a study of the doctor's letter and the time of arrival of the patient at the hospital, it seemed probable that unnecessary delay had occurred. The usual causes of delay are wrong assessment of the urgency of the case, delay in getting ambulances in country districts, and the distances patients have to travel. The last point is brought out in Table II.

TABLE II.—*Distance Travelled by 23 Fatal Cases of Diabetic Coma (1941–50), and the Number Given Insulin Before Being Sent to Hospital*

Distance Travelled	No. of Patients	No. Given Insulin Before Starting
Patients in Oxford City ..	7	2
6–10 miles	4	1
11–15 „	4	0
16–20 „	6	1
Over 21 „	2	0

It is difficult to estimate how long a patient has been comatose before admission. In Table III the duration of the coma in hospital in the 23 fatal cases is shown.

TABLE III.—*Time in Hospital of 23 Cases of Fatal Diabetic Coma*

Time in Hours	No. of Patients
0–1	2
2–12	7
13–24	6
25 or more	7
Unknown	1

We feel that some of the patients would have arrived in better condition if an adequate dose of insulin had been given by the doctor outside.

Insulin.—It is suggested that the doctor sending to hospital a patient with either precoma or coma should adopt the following scheme of emergency treatment.

TABLE IV.—*Showing the Basic Insulin Dosage as Judged by the Reaction of the Urine to Benedict's Test*

Colour of Benedict's Test	Dosage of Soluble Insulin
Red	40 units
Orange	32 ,,
Yellow	20 ,,

(1) Add 20 units of soluble insulin if the ferric chloride test is positive for diacetic acid (N.B., salicylates give a false positive reaction); (2) Add a further 20 units if the patient is drowsy, or 40 units if he is unconscious, from diabetic ketosis; (3) If the patient is unconscious, and circumstances permit, a stomach tube should be passed and the gastric contents aspirated before sending the patient to hospital (Micks, 1948); (4) Carbohydrate should not be given as a "cover" to the insulin.

This scheme is not a substitute for the full treatment of diabetic coma, but is the "first aid" to be applied before the patient reaches hospital, when every hour counts.

A doctor who may have to treat diabetic patients should always have available one bottle of soluble insulin, strength 80 units per 1 ml. Insulin, if stored in a cool place, will maintain its potency for two years.

Summary and Conclusion

The outcome of 111 cases of diabetic precoma and 74 cases of coma admitted to the Radcliffe Infirmary between 1932 and 1950 is presented.

Suggestions are made for improving the prognosis for diabetic patients with progressive ketosis, and stress is laid on the important part that the family doctor can play in improving the outlook for these patients. The prognosis for diabetic precoma is good; the prognosis for diabetic coma is bad. It should be the aim of every doctor dealing with diabetic patients to correct any tendency to progressive ketosis and, if unable to do so, to admit the patient to hospital without delay. Every opportunity should be taken to teach diabetic patients about their disease and how to look after themselves when ill.

REFERENCES

Bruch, H. (1949). *Psychosom. Med.*, **11**, 200.
Joslin, E. P. (1946). *The Treatment of Diabetes Mellitus*, 8th ed. London.
—— (1950). *British Medical Journal*, **1**, 1095.
Marriott, H. L., and Kekwick, A. (1935). *Lancet*, **1**, 977.
Micks, R. H. (1948). *British Medical Journal*, **2**, 200.
Oakley, W. (1949). Ibid., **2**, 1345, 1403.

In December, 1950, a nightly average of 2,239 people slept in reception centres (*Ministry of Labour Gazette*, July, 1951), many of them young men presumably fit and capable of earning their living. During the year the National Assistance Board used for the first time its power to prosecute anyone who had to be helped by the Board because of persistent refusals to work; four men were sent to prison in Birmingham. The effort to help men to settle in jobs has not diminished, and no one was prosecuted without being warned and given another chance.

Medical Memoranda

Ascaris Impacted in Common Bile Duct

Routine stool examination in the hospital laboratory during the last 30 years has shown that ascaris infection among Syrians is almost universal. Ascarides have been found in a liver abscess, in the appendix, and as the primary cause of intestinal obstruction; they have often been suspected of causing cholecystitis. This is the first proved case recorded here of their causing obstruction of the common duct.

Case Report

A woman aged 45 was admitted to hospital complaining of severe epigastric pain, extending towards the left, of eight days' duration. Nausea had been persistent, and for this she had obtained relief by making herself vomit. She had had similar attacks, though not so severe, during the last 30 years.

Physical findings were as follows: no jaundice; acute tenderness over the gall-bladder; temperature 101.3° F. (38.5° C.); pulse 128; B.P. 100/75. Urine: albumin +, chlorides 3 g./l.; W.B.C., 17,500. During the next three days under penicillin and sulphathiazole the temperature settled and the urine cleared. Cholecystography revealed a non-functioning gall-bladder. The abdomen was opened on the fourth day with a diagnosis of subsiding cholecystitis.

Operation.—Under rectal ether, spinal procaine, procaine infiltration, and endotracheal ether and oxygen, an 8-in. (20-cm.) right paramedian incision was made. The gall-bladder was adherent to the duodenum and distended but contained no stones, and the cystic duct up to its junction was perfectly normal. The common duct presented as a thick white cord of the calibre of small intestine arched tensely forwards and outward. It appeared to be the site of some long-standing fibrous change. Suspecting malignancy, the duodenum was mobilized and turned inwards, but no thickening of the ampulla was felt on palpation. Finally it was decided to open the duct. The lumen was found to be entirely filled by a firm white, twisted, cable-like mass consisting of 21 large ascarides. These were removed by forceps and suction. Both hepatic ducts were grossly dilated and one or two worms were removed from the right hepatic duct. The entry into the duodenum was free and dilated rather than constricted. The actual wall of the duct was not thickened, and the appearance of general fibrosis had been produced entirely by the compact mass of worms. Drainage was established by a Y tube snugly stitched round the duct opening, and a second tube was brought out alongside, draining the peritoneal cavity in the region of the duct incision. The liver itself presented many scars on the surface and one fibrous nodule, which was removed for biopsy. The omentum was brought over to wall off the drainage area.

The patient made a smooth recovery. On the tenth day a cholangiography with lipiodol through the intrabiliary tube showed dilated hepatic and common ducts but free passage into the duodenum. Three more worms were evacuated through the common-duct tube. This was removed on the 13th day, and the peritoneal tube on the 17th. There has been no further trouble. Stools contained ascaris ova on the 12th day, but were clear by the 16th after the administration of santonin. Biopsy of the liver showed considerable periportal fibrosis with bile-duct hyperplasia and round-cell infiltration.

Ascarides should always be regarded as a surgical hazard and be cleared out if possible before any laparotomy. The hospital records show at least one case in which ascarides were found free in the peritoneal cavity

(after a partial colectomy), contributing to if not actually causing a general peritonitis. They had evidently forced their way through the suture line. The worm certainly has a predilection for "the narrows."

In yet another case of common-duct obstruction, operated on since the above was written, I found entangled in the biliary sludge and calculi the blackened and compressed remains of a single ascaris.

E. H. R. ALTOUNYAN, O.B.E., *M.C.*, M.D., F.R.C.S., F.I.C.S.
Altounyan Hospital, Aleppo, Syria.

Stress Fracture of the Metatarsal in Childhood

The diagnosis of stress fracture of the metatarsals (march fracture) is rarely made in childhood. Two cases seen during one year at a surgical unit in the Royal Hospital for Sick Children, Glasgow, are here reported.

Case Reports

Case 1.—A girl aged 9 was brought to hospital with a complaint of pain in her right foot of three weeks' duration. There was no history of injury. A year previously she had been treated for an acute osteitis of her right femur which necessitated a period of rest in bed. On examination the dorsum of the foot was slightly swollen, but there was neither redness nor any detectable increase in skin temperature. Tenderness was present along the shafts of the second and third metatarsals. A radiograph (Fig. 1) revealed a transverse fracture of the third metatarsal shaft surrounded by a cuff of callus. This was interpreted as a "march" fracture, and the use of shoes with heavy leather soles was advised. There was rapid subsidence of the symptoms, and later radiographs showed the progress of healing and restoration to normal architecture characteristic of "march" fracture (Fig. 2).

Case 2.—A boy aged 6½ had a pain in his right foot of one week's duration. There was no history of injury, of any previous bony infection, or other illness. Examination revealed slight swelling of the dorsum of the foot, local heat, but no redness. There was tenderness along the second and third metatarsal bones, and *x*-ray examination revealed a slight raising of the periosteum of the second metatarsal.

FIG. 1.—Case 1. Fracture with callus of third metatarsal. Note sesamoid bones at head of first metatarsal.

FIG. 2.—Case 1. Note backward continuation of first intermetatarsal space.

On these criteria a diagnosis of acute osteitis was made. At operation, however, the periosteum was found to be intact and healthy, and there was no evidence of any pus formation (suggesting that the diagnosis was not correct). With rest in bed the swelling and pain subsided, and a radiograph one week later revealed a transverse fracture of the shaft of the second metatarsal with the cuff of callus characteristic of "march" fracture. Later *x*-ray films showed the same restoration to normal bony architecture as in Case 1.

Comment

The aetiology of stress fracture of the metatarsals is obscure. Predisposing factors suggested are a developmental structural weakness, muscular inefficiency, and trauma. Morton (1927) has described four signs or defects seen on *x*-ray examination which, he maintains, indicate a potentially weak foot. Dodd (1933), studying a series of 14 radiographs of "march feet," found one or more of these defects in each case. In the present series several of Morton's signs were present. Barns (1943), discussing the condition as found in Service recruits, stated that "it tends to occur in recruits who led inactive lives before entry into the Service. This must therefore be accepted as the predisposing cause." Inactivity in the sense implied is almost unknown in childhood, but in Case 1 the period of immobilization made necessary by the infection of the femur might conceivably have produced a muscular hypotonicity sufficient to permit damage to a potentially "weak" foot. Lastly, though no history of injury was obtained in either of the present cases, it should be remembered that the history in childhood is often unreliable.

I wish to thank Mr. Matthew White for his helpful criticism and for permission to publish these two cases.

DUNCAN A. MACPHERSON, M.B., Ch.B., F.R.F.P.S.G.

REFERENCES

Barns, H. H. F. (1943). *British Medical Journal*, **2**, 608.
Dodd, H. (1933). *Brit. J. Surg.*, **21**, 131.
Morton, D. J. (1927). *J. Bone Jt Surg.*, **9**, 541.

Reviews

FRIEDRICH VON MÜLLER

BY

Sir HENRY SOUTTAR, C.B.E., D.M., M.Ch., F.R.C.S.
Consulting Surgeon, London Hospital

Friedrich Müller was born in 1858 and lived for 83 years. His life therefore covered the whole period of the growth of modern Germany, and as it was a very full life, inspired by a deep devotion to his profession, his autobiography[1] is of absorbing interest. He describes the life of the German student, his difficulties and his ambitions, with all the understanding of personal experience. We follow him through an arduous training, very different from our own, till he emerges after long years of assistantship as a lecturer and finally as a professor. Surrounding all this is a picture of German life as it affects the student, masterly in its simplicity and in the acute observation which it almost conceals.

Müller was born in Augsburg, where his father, the fourth of a line of doctors, was on the staff of the local hospital. At 18 he entered the Technical High School in Munich, and two years later joined the medical school there, where he studied chemistry under Emil Fischer. At 22 he took advantage of a family privilege to go to Tübingen for a year, and there he accompanied Jürgensen, the head of the polyclinic, in visits to patients in the poorer quarters of the town and in the neighbouring villages. The popularity of the visits, he thinks, may have been due to the doctor's faith in alcohol, which he lavishly prescribed.

A year later he entered Gerhardt's clinic at Würzburg and began the serious study of medicine. Gerhardt lectured in his theatre to a large body of students, and his intense sympathy with his patients and the clarity of his teaching made a great impression on Müller, and indeed formed the pattern of his own future work. "The presentation of every case formed a complete whole and gave a living picture of the patient, of his troubles, and of his treatment." Gerhardt in 1880 was in advance of his time in urging removal of the appendix, and the fact that von Bergmann was his surgical partner was a great advantage.

After a vacation spent as a dresser with his father in Augsburg he returned to Munich for classes before his examination. But after Würzburg he was not impressed by Ziemssen, who sat by his patient's bed and yawned, or by Nussbaum, who operated in a frock coat, although it was covered by an apron. But he found a man after his own heart in Gudden, the great neurologist, "who ruled among his patients like a king and presented us with problems but never with a dogma." He never forgot how Gudden took him, "a young student," to his own laboratory and showed him the sections of the brain by which he had discovered the mechanism of the pupillary reaction to light. He passed his examinations with ease, but he remarks that such State examinations were often perfunctory, for it sometimes happened that one examiner was deaf and the other never read the papers.

[1] *Lebenserinnerungen.* By Friedrich von Müller. (Pp. 264; illustrated. M. 15.) Munich: J. F. Lehmanns. 1951.

Koch's Bacillus

In 1882 he was appointed an assistant to Gerhardt's clinic at Würzburg at a salary of 80 marks a month, to which his father added 50 marks so that he could live carefree. Typhoid was very prevalent, and 30% of the nurses and maids became infected. Cross-infection of the patients was common and often fatal. It made a great impression on him, and led to the strict isolation of typhoid cases when in later years he was professor at Basle. In 1882 Koch announced his discovery of the tubercle bacillus to the Physiological Society in Berlin, but not to the Medical Society because of the opposition of Virchow. Müller always looked back on this as the great event of his assistant days, and he was able to find the bacillus in miliary tubercles in lungs and in glands. Gerhardt provided him with an immersion microscope, and his work on this formed the basis of his first publication, a communication to the Würzburg Medical Society.

His chief interest, however, was in metabolism, especially in jaundice, and in the complicated chemical problems involved. The three and a half years which he spent with Gerhardt at Würzburg were indeed the basis of all his future work. The relations between the professor and his assistant are shown in that both their names appear on a volume of *Transactions* of the Würzburg Medical Clinic, a rare honour never to be forgotten.

In 1885 Gerhardt was called to the Charité Clinic at Berlin, and Müller went with him as assistant. With him in Berlin was Paul Ehrlich, who was already engaged in his epoch-making work on the staining of bacteria and blood films. With Leyden, Bordeleben, and Henoch the staff of the Charité formed a remarkable group. His salary was now only 30 marks a month, and even with 50 marks from his father life was difficult. But a small medical pocket manual was an immediate success, while his private class reached the number of 300 and relieved him of all anxiety. On Gerhardt's advice he applied for recognition as a lecturer. To read a paper before Virchow, Koch, Waldeyer, and the whole staff must have been somewhat of an ordeal in spite of the encouragement of the dean, Du Bois-Reymond, and somewhat of a contrast to his first public lecture, when a solitary Japanese was his whole audience.

English and American doctors were, however, crowding to Berlin. Müller saw his opportunity and, horrified at their appalling German, managed to lecture to them in English. In after years he reaped the benefit when he travelled to England and America, but later still a protest came from the Ministry against the use of any language but German. Meanwhile he had the full support of Gerhardt, who in 1899 sent him on a visit to England, where he spent two months visiting the Royal Colleges, Bart's, Guy's, and the British Museum. On his return he found that his success as a teacher had attracted the attention of Althoff, the Minister of Culture, and he was called to Bonn as a professor. The salary was only £90 a year, but the status of professor was worth the sacrifice.

Professor of Laryngology

At Bonn, as he had no beds and a very limited field of work, he decided to start a course in laryngology, and equipped himself with the necessary instruments. To his surprise the class was a great success and crowded

with students from every department of the university, largely non-medical. The reason only appeared later—that it was the cheapest class for which a student could be signed up. It is of interest that one of his pupils was Aschoff, and his colleague in the department of physics was Hertz. But there was little scope at Bonn, and in 1890, on the request of Althoff and the advice of Gerhardt, he transferred to Breslau as professor of laryngology.

In Breslau he was received into a very distinguished and friendly circle, which included Heidenhain the physiologist, Mikulicz the surgeon, Forster the ophthalmologist, Wernicke the neurologist, and Neisser the bacteriologist. At first there was no opening for him in the hospital, but in spite of this he started classes in laryngology and auscultation, providing clinical material from the workhouse at twopence each an hour. His classes were so successful that accommodation was found for him in the hospital, where he was soon established as a regular professor and rapidly developed a large and lucrative practice. It was with great regret and only under official pressure that in 1892 he moved to Marburg.

The polyclinic of Marburg gave him no beds, but included the charge of patients in the poorer quarter of the town, so that he was able to give his students clinical experience. He was made very welcome in the university circle, marrying the daughter of the professor of surgery and later becoming dean of the faculty. The German medical curriculum was being reorganized, and he attended conferences under the chairmanship of the great anatomist, William His of Leipzig. After seven busy years he was called to Basle in 1899.

In Basle for the first time, at the age of 41, he had beds and the control of a complete medical clinic. He was now able to pursue his work on metabolism under good conditions, and his teaching was stimulated by an enthusiastic group of students, who included Staehelin and Abderhalden.

In 1902, however, he was invited almost simultaneously to three chairs of the highest distinction—in Munich, Berlin, and Vienna. The position must have been without parallel. Largely for family reasons, he chose Munich, and there he spent the rest of his life.

Research and Lecturing

Müller now had excellent facilities for research and teaching. He deliberately chose the students in their first clinical years as his special province, leaving the more advanced classes to his colleague Josef Bauer. His classes were large, and he lectured to three or four hundred students, but he planned his lectures as lecture-demonstrations and took infinite pains that every student should both see and hear every detail. Following the example of his great teacher Gerhardt, he presented each case or subject as a whole, with all the clinical and pathological detail required for full comprehension of its meaning and significance. Siemerling and Weigert had placed at his disposal a fine collection of neurological material, especially sections of the brain and spinal cord, and, as there was no special neurological department, he had ample cases in his own clinic. With three assistants who came with him from Basle he continued his own researches on metabolism, and he was thus able to cover a large field of medicine from an original standpoint. A series of investigations into the physical origin and the precise meaning of the sounds elicited in auscultation, of breathing and of the heart, reveals his genius for detail and for the clarity which was characteristic of his teaching.

In 1897 he was invited to lecture in America, and he visited many of the clinics in the U.S.A. His description of all that he saw reveals acute observation and a wonderful knowledge of the English language. In 1911 he was invited to give evidence to the Haldane Commission on Medical Education, and he took the opportunity to visit Oxford, where he stayed with Osler and was present at the Encaenia. With Osler he had much in common, and they formed a close and lasting friendship.

In 1913 he came over to the meeting of the International Medical Congress in London. On the proposal of Waldeyer, Munich was chosen for the next meeting in 1917, and Müller was elected president. In 1914, "at a time when we believed that we lived in the fullest peace," he was elected rector of the University of Munich. At the end of July, 1914, he was called in consultation to a German patient near Windsor, and he just managed to reach Germany before everything was dissolved in war.

After the war he paid a long visit to America and several visits to England, and took a leading part in many international conferences. He knew as intimate friends a great number of the leaders of medicine, and he must have exerted a profound influence on medical thought. He remained throughout passionately devoted to Germany and to its mode of life, but it was a devotion we can all admire, without any trace of self-interest, full of appreciation of the achievements of others and deeply valuing their friendship. There have been few greater ambassadors for medicine and for its highest ideals.

For all those who are interested in the teaching of medicine his life deserves careful study, for they will find in him the rare combination of a great clinical teacher and a great clinician. If they can convey to their students something of the spirit which inspired Friedrich Müller they will not have taught in vain.

INBREEDING

The Theory of Inbreeding. By Ronald A. Fisher, Sc.D., F.R.S. (Pp. 120. 10s. 6d.) Edinburgh and London: Oliver and Boyd. 1949.

Inbreeding and its effects have long been a topic of much interest to mankind, if we may judge by the misapprehensions and myths that have become so widely propagated in the absence of evidence from experiment. That inbreeding has indeed a real biological significance cannot be doubted by anyone familiar with the many devices, ranging from the floral structures of plants to the ancient incest taboos of man, which are adapted to its regular avoidance—or, in other cases, to secure its regular occurrence. The experimental attack (as offered to the speculative discussion) on inbreeding began with Charles Darwin, and since his time, especially during the half-century of genetical science, we have come to learn something of its consequences. But we need to know much more if we are to be able to measure its progress, to use it efficiently as a tool in our plant and animal breeding, and to understand fully its importance for the constitution and evolutionary prospects of living species, including our own.

Professor Fisher briefly discusses the history and importance of inbreeding in his first chapter before turning to the more technically genetical and mathematical questions which arise in its study. He is chiefly concerned with means of evaluating the genetical effects and progress of inbreeding under diverse systems of mating and diverse systems of genic organization. For this purpose he makes use of a matrix algebra which, in spite of his care in setting out and exposition, most biologists and medical men will inevitably find difficult going. He concludes with appendices on the special problems of inbreeding programmes in species bearing single offspring at a birth, on the efficiency of certain devices by which inbreeding is avoided in plants, and on the importance of inbreeding in crop and stock improvement. No especial attention is given to man, and indeed the discussion centres essentially on experimental inbreeding in other species.

This book is a major contribution to the study of the subject. It deals with complex methodological problems which arise in genetical research, and is primarily a book for the specialist.

K. MATHER.

GYNAECOLOGY FOR GENERAL PRACTITIONERS

Practical Gynecology. By Walter J. Reich, M.D., F.A.C.S., F.I.C.S., and M. J. Nechtow, M.D. (Pp. 449; 187 illustrations, including 55 subjects in colour. £4.) Philadelphia and London: J. B. Lippincott. 1950.

This is one of several textbooks from the U.S.A. in recent years which presents what may be described as the new approach to gynaecology. At least it emphasizes the many important minor gynaecological problems and symptoms which confront the general practitioner, and which, during the development of gynaecological surgery, have sometimes failed to receive the attention they deserve from those responsible for teaching undergraduates.

The relation between gynaecology and social and psychological medicine is well stated, and there are sections on marital guidance and contraception. Clinical methods and medical treatment, including hormone therapy, are described simply and rationally. The authors omit details of all operations falling outside the scope of the general practitioner. There comes a point, however, when omissions cease to be praiseworthy, and on some matters there is not quite enough information to enable a student to pass a British qualifying examination. It may serve him better when the examination is passed. In any case he will need to have been in practice a few years before being able to save enough to pay the high price it bears in this country; not even the excellent illustrations and 15 colour plates compensate for this.

T. N. A. JEFFCOATE.

DRUG ERUPTIONS

Die Nebenwirkungen der Arzneimittel auf die Haut. By Dr. Julius Mayr. (Pp. 162; 147 illustrations. M. 13.50.) Jena: Gustav Fischer. 1950.

This small textbook on drug eruptions is written by an experienced clinician who directed a dermatological department at the University of Munich for many years. The number of drugs now in common use is considerable, and as most of them can cause eruptions of various types a book attempting to cover the field is welcomed, especially as the author has taken much trouble to give detailed descriptions of eruptions due to drugs used in Germany and other countries.

He discusses, in three chapters respectively, the pathogenesis of drug eruptions, the local effect of drugs on the skin, and the effect of drugs administered by mouth or parenterally. There are 45 sections on groups of drugs such as purgatives and sedatives, as well as on individual drugs; heavy metals, halogens, and antibiotics are considered at length. The printing and paper are good, and there are 147 illustrations, several being in colour, though these are not of so high a quality. The book contains 700 references, and this list combined with the low price makes it a useful book to keep on the shelf for information.

H. HABER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Advice to the Expectant Mother on the Care of Her Health and that of Her Child. By F. J. Browne, M.A., D.Sc., F.R.C.S.Ed., F.R.C.O.G. 9th ed. (Pp. 50. 1s.) Edinburgh: E. and S. Livingstone. 1951.

The Pharmacology and Therapeutics of the Materia Medica. By W. J. Dilling, M.B., Ch.B., M.P.S. 19th ed. (Pp. 598. 21s.) London: Cassell. 1951.

The Differentiation of Escherichia and Klebsiella Types. By F. Kauffmann, M.D. (Pp. 57. 15s.) Oxford: Blackwell Scientific Publications. 1951.

Emotions and Clinical Medicine. By S. Cobb, M.D. (Pp. 243. 15s.) London: Chapman and Hall. 1950.

Accepted Dental Remedies. Issued by the American Dental Association. (Pp. 207. $1 50.) Chicago: American Dental Association. 1951.

The Enzymes: Chemistry and Mechanism of Action. Edited by J. B. Sumner and K. Myrbäck. Vol. 1, part 2. (Pp. 636. $12.80.) New York: Academic Press. 1951.

Pasteur et la Microbiologie. By A. Delaunay. (Pp. 134. No price.) Paris: Presses Universitaires de France. 1951.

La Mesure de Rendement Cardiaque en Clinique. By A.-H. Israël. (Pp. 154. 600 francs.) Paris: L'Expansion Scientifique Française. 1951.

Le Foie Diabétique: Aspects Hormonaux. By Dr. J. Mirouze. (Pp. 365. 1,300 francs.) Paris: L'Expansion Scientifique Française. 1951.

De Psychologie van het Ongevalsgebeuren. By Dr. W. Winsemius. (Pp. 187. 6 florins.) Leyden: H. E. Stenfert Kroese's Uitgevers-Mij. 1951.

The story of the struggle of Miss Jex-Blake and her companions to become the first female medical students of Edinburgh University in the 'seventies is told in the novel by Muriel Masefield. *Seven Against Edinburgh* (Heinemann; 10s. 6d.; pp 324). The author brings a fictitious character and her family into the famous *Septem* to aid the narrative, but she has kept painstakingly to facts and, in parts, to true conversations. Indeed, her keenness for veracity occasionally tinges the text with awkwardness. The seven ladies fought vigorously with the intransigent university authorities. They were obliged to repel suggestions that they would filch the male doctors' livelihoods and that the study of medicine would "unsex" them, and had to suffer some attacks by the men students. Mrs. Masefield's style sometimes swings more towards Ayres than Austen, but she has written an accurate and sensitive story. It will have its greatest attraction for women readers.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY AUGUST 11 1951

HUMAN FUNGAL INFECTIONS

A century ago the recognition of the mycotic nature of certain common superficial infections of the skin stimulated speculation on the role of fungi in other disorders. The rise of bacteriology and the appreciation of the part played by protozoa and viruses in the aetiology of major diseases led to a changed outlook, and even to-day many practitioners consider ringworm and medical mycology to be synonymous terms. Although ringworm is still ubiquitous, this viewpoint can no longer be maintained. A number of important systemic mycoses have been described in various parts of the world, and the survey carried out by Duncan[1] during the war suggests that in this country, too, pathogenic fungi are not an exclusive concern of the dermatologist.

The best-known systemic fungal infection is actinomycosis, which, as Cope has said, has been diagnosed "wherever there is a microscope and a laboratory." Unfortunately, microscopical findings have too rarely been supplemented by critical cultural studies, with the result that it is not yet certain whether the same or different organisms are responsible for actinomycosis in man and in cattle. The human and bovine strains are probably distinct, and the problem is at present being investigated by Mrs. Dagny Oxford at Aberdeen as a project sponsored by the Medical Research Council.

The most familiar of the systemic mycoses proper is moniliasis. This, like actinomycosis, is an endogenous disease with a world-wide distribution. Most of the important generalized mould infections, however, are of exogenous origin, and this is usually correlated with a more limited geographical distribution. Coccidioidomycosis has a focus in the warm arid regions of the United States and is rare elsewhere. (The only British case was a laboratory infection.[2]) South American blastomycosis, as the name suggests, is also geographically localized. Other systemic mycoses are more widespread, as, for example, sporotrichosis (*Sporotrichum schencki*), which in its classical form is an infection of the lymph nodes, resulting in a succession of ulcers along a lymphatic vessel. This disease, which has occurred sporadically in Britain for the past 40 years, is usually diagnosed without difficulty. Two other diseases, torulosis (*Cryptococcus neoformans*) and histoplasmosis (*Histoplasma capsulatum*), which have both been recorded for Britain, where they may be endemic, are much more elusive. The former is characteristically a disease of the central nervous system. It frequently takes the form of a meningitis or meningo-encephalitis, and may be confused with tuberculous and other forms of subacute meningitis. There are published records of approximately 150 cases from all parts of the world, and the frequency with which the diagnosis has been made after death suggests that the incidence may be higher than these records indicate. "If any treatment favourably influences the course of torulosis, it is unknown," according to Cox and Tolhurst,[3] and the same applies to histoplasmosis, of which an apparent endemic case was noted recently in this *Journal*,[4] although in parts of the United States a mild and perhaps subclinical form appears to be widespread.

Most of the systemic mycoses hitherto described may affect the lungs, and the examination of sputum (by the methods detailed in a useful paper by Conant[5]) is one of the routine duties of a medical mycologist. The detection in sputum of the capsulated budding cells of *C. neoformans* or of a mononuclear cell parasitized by *H. capsulatum* is presumptive evidence that these fungi are present as pathogens, but the right interpretation of the presence of many other fungi is usually a matter for judgment in the light of all aspects of the case. Species of *Candida*, *Aspergillus*, and *Geotrichum* are often found in sputum of apparently normal persons, and while these fungi are sometimes primary pathogens they are more frequently secondary invaders. Evidence of pathogenicity to experimental animals is of little value in deciding whether such a fungus is the cause of disease in a human case, for the saprophyte as well as the parasite frequently behaves as a pathogen in a laboratory animal. Neither the mycologist nor the clinician alone is usually in a position to come to a correct decision. Mere isolation of a potentially pathogenic fungus may mean nothing, and both the clinical aspects of the case and the oecology of the organism must be considered.

The factors which determine pulmonary infections are still obscure, but for other conditions there are clues. Vaginitis caused by *C. albicans*, for example, is most prevalent in pregnant women, especially

[1] *British Medical Journal*, 1945, **2**, 715.
[2] Nabarro, J. D. N., *Lancet*, 1948, **1**, 982.
[3] *Human Torulosis*, 1946, Melbourne University Press.
[4] Limerick, C. B., *British Medical Journal*, 1951, **1**, 885.
[5] *Amer. Rev. Tuberc.*, 1950, **61**, 690.
[6] See Rothman, S., *Trans. N.Y. Acad. Sci.*, 1949, Ser. II, **12**, 27, for further details and other examples.

during the last three months before labour. This is probably due to the temporary increase in glycogen in the vaginal mucosa at this time, there being spontaneous recovery after delivery. Moniliasis of the skin, which is usually confined to the third interdigital space, is an occupational hazard of housewives and bartenders, whose hands are constantly in and out of water. The same disease is prevalent among sufferers from diabetes, and of these obese women are the worst: infection in them may extend to all the main intertriginous areas of the body. A prevailing feature of these sites is high humidity, and in some individuals there is a tendency for the horny layer to be macerated by sweat, but generalization of the infection seems to be also dependent on the disturbed carbohydrate metabolism. A common explanation of the phenomenon is that there is an increase in the glucose content of the skin in diabetes.[6] Age is clearly a factor in some mycotic conditions, and the higher incidence of mycoses in men than in women, probably from several unrelated causes, is remarkable.

The true importance of fungal infections has still to be decided in this country and in others where the general awareness of the pathogenic possibilities of fungi lags far behind that prevailing in the Americas. Progress in this direction is likely to be very slow, for there is still no adequate provision in the British Isles for instruction in medical mycology, either at an undergraduate or at a postgraduate level, and yet in the opinion of Professor David T. Smith, —who comes from Duke University, North Carolina, the most important teaching centre for medical mycology in North America, and who may therefore, some may think, be biased—" mycotic infections occur with sufficient frequency to justify their consideration in the differential diagnosis of every difficult and complicated pulmonary and systemic infection."

TUMOUR-CELL EMBOLISM

The fact that emboli composed of normal tissue cells occur from time to time has been known for over half a century. Those who had to treat casualties during the war became familiar with the abrupt onset, in a small number of cases, of grave signs and symptoms of damage to the central nervous system, due to the lodgment in the small vessels of the brain of innumerable fat particles from the injured tissues. These emboli are also found in the liver and kidneys. Fat embolism is specially common in the lungs after serious injury, and may even be found after simple skull fracture and soft-tissue injuries, including surgical operations on the obese abdomen. Robb-Smith[1] has described a simple post-mortem technique for the demonstration of these emboli. Injury to other normal tisues—brain, liver, and red bone marrow—can give rise to emboli composed of cells from these tissues, and embolism from placental trophoblast may occur. The practical problem which arises is whether trauma may be important in disseminating malignant tumours. Metastasis of a carcinoma is usually attributed to the invasive powers of the malignant cell, which gains access to vessels, principally lymphatics, by virtue of these properties. Perhaps this conception may have prevented more thought being given to simple mechanical processes in which the cancer cell plays a merely passive role and which may endanger the life of the sufferer from malignant disease. With sarcoma it is already suspected that rough handling can initiate metastasis.

Young and his co-workers[2] in Aberdeen, using an ingenious technical method and a transplantable testicular tumour in the rabbit, have shown that the interstitial pressure, or " tissue pressure," within a malignant tumour rises steadily with increase in size, at least until necrosis precludes further measurements. Tissue pressures are difficult to record accurately, and an essential preliminary step in this research was to ensure that constant results were obtainable in a healthy testis. It was soon found that gentle squeezing of the organ caused, as would be expected, a considerable rise in tissue pressure, as it did also within the tumour in the contralateral testis. Much greater rises in pressure were recorded after injection of small quantities of saline. In earlier experiments Young and Griffiths[3] used a model to reproduce the relationship obtaining between parenchyma and vasculature in both normal and pathological tissues. This model consisted of a collapsible tube of thin rubber traversing horizontally a viscous medium containing suspended polystyrene beads or fragments of a gel. When a small hole was present towards the distal end of the collapsible tube the external particles entered the tube readily in great numbers as soon as there was a relatively slight increase in " extravascular " pressure and before the tube had time, as it were, to collapse. In fact, in certain easily obtainable conditions the wall of the tube could be made to oscillate and thereby apparently to encourage the entry of particles. Further, any " exudate " from within the tube returned *in toto* under the same conditions.

[1] *Lancet*, 1941, **1**, 135.
[2] *J. Path. Bact.*, 1950, **62**, 313.
[3] Ibid., 1950, **62**, 293.
[4] *Lancet*, 1949, **2**, 973.
[5] *Amer. J. Surg.*, 1935, **27**, 26.

The practical implications of these experimental results are important, for it may be that some clinical manœuvres employed in everyday practice in the diagnosis and even in the treatment of malignant tumours increase the risk to the life of the patient. Even palpation may not be innocuous, since the Aberdeen workers have shown that digital pressure far less than that often exerted in clinical examination causes a large rise in tissue pressure. Heavy-handed and repeated examinations are therefore contraindicated. As to needling, whether it be aspiration biopsy or injection of local anaesthetic, the forcible introduction of an instrument, however fine, will cause a rise in pressure without any injection being made, and the tearing of small vessels will allow tumour cells to gain entrance within them. It would appear, therefore, that aspiration biopsy is as dangerous a manœuvre as its result is difficult to interpret, and needling of lymph nodes in particular might well be limited to the diagnosis of early trypanosomiasis. Biopsy with the surgical knife must obviously continue to be standard practice in selected cases, but it is still carried out when its results may be valueless or even misleading, as cited by Brailsford[4] and by Ewing[5] in the case of tumours of bone. It remains to consider whether existing records might be statistically examined in an attempt to settle the merits or demerits of the various clinical methods. For instance, it might be instructive to compare the survival rates of stage 1 breast carcinomas with and without initial biopsy.

THE MINISTERS' REPLY

At its meeting on July 19 the Special Conference of Representatives of Local Medical Committees decided to request the Minister of Health to refer to arbitration "the determination of the proper size of the Central Pool, having regard to the recommendations of the Spens report and to present-day money values, such arbitration to be arranged without further delay."[1] The Special Conference also adopted the G.M.S. Committee's recommendation that, once the size of the Central Pool had been determined by arbitration, discussions on the form of distribution should be resumed with the Minister.

In the reply from the Ministry, which has been made public and is published in this week's *Supplement*, it is observed that the Ministers have agreed to withdraw their previous proposal, to which exception was taken, and to consider the matter afresh. The Ministers consider that it is of first importance to devise a new plan for the distribution of the Central Pool in order to "safeguard the standard of medical services by discouraging unduly large lists and at the same time to bring about the relative improvement in the position of those practitioners least favourably placed under the present plan of distribution, to make it easier for new doctors to enter general practice, and to stimulate group practice." To this end the Ministers suggest the immediate establishment of a working party. If this is agreed the Ministers will, it is stated, be prepared to seek, in agreement with the G.M.S. Committee, a decision by an independent adjudicator on the sum which should be used in calculating the size of the Central Pool. In calculating this, account will be taken of remuneration received by general practitioners from all sources "in order to give effect to the recommendations of the Spens Committee, having regard both to the change in the value of money since 1939 and to the increases which have taken place in incomes in other professions." The adjudicator, who is to be appointed by agreement between the Ministers and the G.M.S. Committee, will be asked to decide the date from which any new sum should apply.

It is considered that both investigations—that is, by working party and by adjudicator—would proceed simultaneously, "though it is appreciated that it may not be possible for a new plan of distribution to be finally settled until the future size of the Central Pool is known." Finally, the letter states that, subject to the overriding authority of Parliament, the Minister of Health and the Secretary of State for Scotland will accept the adjudicator's decision provided the G.M.S. Committee undertakes now to accept whatever decision may be reached, and provided, too, that both sides agree on a revised plan for distributing the Central Pool newly calculated.

A special meeting of the G.M.S. Committee has been called for Wednesday, August 15, to consider the reply of the Minister of Health and the Secretary of State for Scotland summarized above. It may be noted that the Ministers have not asked that the matter should be referred to Whitley Committee A—a course of action, it may be presumed, which would have prolonged investigation into the profession's case. Whitley Committee A has not, in fact, yet met; in any event there is no agreed method of arbitration if the conciliation machinery of Whitley breaks down. It may be noted, too, that the letter refers not to an arbitrator but to an adjudicator. Perhaps the latter word has been suggested because there is no disagreement between the profession and the Ministry about the acceptance of the recommendations of the Spens report—a summary of which it is hoped to give in next week's *Supplement*. According to the Oxford Dictionary, an adjudicator is "one who adjudicates; who settles a controverted question or awards the prize in a competition."

[1] *British Medical Journal Supplement*, July 28, 1951, p. 29.

MEGACOLON

The management of megacolon in childhood has been difficult in the past because of uncertainty about its aetiology, but recent reports from workers in Britain and the U.S.A. have led to a rational classification of the condition into symptomatic megacolon, idiopathic megacolon, and Hirschsprung's disease. In symptomatic megacolon a gross obstruction is demonstrable; this may be due to a stricture, stenosis, tumour, or nerve lesion, such as is associated with spina bifida. The treatment, of course, is to remove the cause of obstruction. In childhood cases of idiopathic megacolon form the largest group. The condition is probably acquired as a result of faulty bowel habits, fissure in ano, or other minor causes which lead to gradually increasing passive distension first of the rectum and then of the sigmoid colon. Radiological evidence of dilatation of the anal canal and rectum (terminal reservoir type) or of part or all of the sigmoid colon (tubular dilatation type) differentiates this group clearly from true Hirschsprung's disease. The condition is essentially benign and responds to persistent conservative treatment, including bowel washouts. Hirschsprung's disease forms the third group in this classification. The abnormality in this serious congenital disorder has been traced to the terminal segment of intestine, which is of normal or slightly narrowed calibre, while above it the bowel is dilated and hypertrophied. Diagnosis now depends on the radiological demonstration of the normal calibre of the rectum and part or all of the sigmoid colon. The pathological changes eluded detection for a long time. Only by microscopical examination of the terminal part of the intestine can it be seen that the ganglion cells of Auerbach's and Meissner's plexuses are missing. The resulting lack of co-ordinated peristaltic movement causes secondary dilatation and hypertrophy of the bowel proximal to the abnormal segment. In the light of this new aetiological conception the rational treatment of Hirschsprung's disease is resection of the aganglionic distal segment by rectosigmoidectomy. Lee and his colleagues[1] in the U.S.A. have paid a tribute to the work of Bodian, Stephens, and Ward at the Great Ormond Street Children's Hospital for making "intelligent selective treatment [of megacolon] possible." These British workers[2-4] have now demonstrated the essential histopathological lesion in 40 cases. Similar findings have been reported in the U.S.A.,[1 5-7] and in this country Burnard[8] has discussed the features of the disease in young infants. Swenson and Bill[9] were the first to devise rectosigmoidectomy as a treatment for Hirschsprung's disease. Their method was adopted and slightly modified by Stephens,[2] working at Great Ormond Street. The long-term results of this treatment over a period of two to three years have been remarkably good.[4 10]

Bodian, Carter, and Ward[4] have also recently reported a genetic study of Hirschsprung's disease, and though they have not yet been able to define the mode of genetic determination they were able to put forward evidence showing that the chances of a male sibling of a known case developing Hirschsprung's disease were about 1 in 5. The chances of a sister being affected were much smaller. In this disease the length of the aganglionic segment may vary; in a small number of cases it can be considerably longer than the rectum and sigmoid. Bodian and his colleagues point out that a genetically determined disturbance may occur at any stage of differentiation of intestinal nerve cells, which, they suggest, usually proceeds in a cranio-caudal direction. Thus, larger or smaller aganglionic segments would be produced according to early or late interference with normal embryological development.

1 *Surg. Gynec. Obstet.*, 1950, **91**, 281.
2 *Lancet*, 1949, **1**, 6.
3 Ibid., 1950, **1**, 19.
4 Bodian, M., Carter, C. O., and Ward, B. C. H., ibid., 1951, **1**, 302.
5 Whitehouse, F. R., and Kernohan, J. W., *Arch. intern. Med.*, 1948, **82**, 75.
6 Zuelzer, W. W., and Wilson, J. L., *Amer. J. Dis. Child.*, 1948, **75**, 40.
7 Swenson, O., Rheinlander, H. F., and Diamond, I., *New Engl. J. Med.*, 1949, **241**, 551.
8 *British Medical Journal*, 1950, **1**, 151.
9 *Surgery*, 1948, **24**, 212.
10 Swenson, O., ibid., 1950, **28**, 371.

THE ATOM AND THE CRIMINAL

Nuclear physics has just produced a new weapon to beat the murderer. It is a method which will measure the amount of arsenic along the length of a single hair, and so yield a diary of chronic poisoning; and it depends on radioactivation analysis, which was discussed at a recent meeting of the Physical Methods Group of the Society of Public Analysts. The idea is in principle simple enough. An atomic pile produces many neutrons, the particles which along with protons form the greater part of the nucleus of every atom; and the slower moving ("thermal") neutrons released from uranium in a pile may be captured by the nuclei of foreign atoms on their track. Thus ordinary arsenic contains atoms of a single stable isotope, As^{75}, but when it captures neutrons it becomes a new isotope, radioactive As^{76}, which begins at once to decay and to shoot out electrons (β rays) and γ rays, rather like radium. This radiation is characterized in two ways, by the rate at which it is emitted (the decay in this case is half over in 26.8 hours), and by its spectrum—certain specified wavelengths of γ rays, and certain speeds of travel of the electrons. Atoms of the different elements differ in the ease with which they capture neutrons, and this provides the other important variable in the analysis. Arsenic does it particularly well, but many of the atoms composing a hair do not—for instance, carbon, oxygen, nitrogen, and hydrogen. Sulphur is probably the chief competitor, but the decay rate of the radioisotope it produces is quite different, and so is the spectrum of emitted radiation.

In practice, therefore, the suspect hair is exposed to neutrons in an atomic pile, and when it has become suitably radioactive the electrons it emits are studied with a Geiger-Müller counter through various thicknesses of an absorbing filter. Localization is determined by cutting the hair into short lengths, or by moving it across behind a narrow slit in some heavy shielding material, or possibly by its direct effect when laid on

an unexposed photographic plate (autoradiography). Less than one part per million of arsenic is easily detected.

This method cannot be used to measure arsenic in body fluids such as blood because of interference from the sodium, Na^{23}, always present, which picks up slow neutrons fairly easily, the resulting Na^{24} having a half-life of only 15 hours and also emitting β and γ rays. It has, however, been used to measure the amount of sodium and potassium inside a single nerve fibre before and after activity. R. D. Keynes described how the nerve was irradiated for a week inside a sealed quartz tube at Harwell, then emptied into a nickel dish and its radiation measured with a Geiger counter, first through a thick filter which passed only γ rays from Na^{24}, then through a thin filter which in addition transmitted the powerful β-radiation from the decay of K^{42}. Radio-activation analysis is thus a very sensitive technique for chemical analysis, likely to have other forensic uses and other applications in medicine.

SODIUM RESORCYLATE

Stockman showed in 1920 that salicylic acid, which is chemically the *ortho-* form of hydroxybenzoic acid, differs from the *meta-* and *para-* forms of this acid in that it alone is of value in the treatment of rheumatic fever. Elsewhere in this issue Drs. Reid, Watson, Cochran, and Sproull suggest that this might be because the –COOH and –OH groups were adjacent and might form a ring by a process called chelation. They have tested their view by giving γ-resorcylic acid to patients with rheumatic fever, since this is an acid in which not only one but two additional rings might be formed. They have found that this acid has a beneficial action and that in amounts of 1 g. daily it is similar in effect to 10 g. daily of salicylic acid.

Unfortunately, resorcylic acid, besides benefiting rheumatic fever, has various other effects which are drawbacks to its use. After the third day of taking it, four patients showed emotional instability and became confused; they also suffered from pains in muscles and joints. For this reason it is unlikely that resorcylic acid will replace salicylic acid, but the results obtained give support to the hypothesis with which the investigation started.

It appears, moreover, that sodium resorcylate has various actions which resemble the effects of A.C.T.H. and cortisone. For example, Professor Buttle has found that when formaldehyde is injected into the pad of the mouse's foot a swelling of the leg follows. This is reduced when either A.C.T.H. is given or when resorcylic acid is given. This is obviously a promising observation, which suggests that salicylates may act in rheumatic fever by causing a liberation of A.C.T.H. from the pituitary gland. Salicylates are clearly not very efficient in this respect since they do not benefit rheumatoid arthritis to any extent. Nevertheless, the clue must be followed, for it may be the path which leads the way to what so many are seeking—namely, a substitute for cortisone of much simpler structure.

CONVALESCENCE

Few aspects of medicine have been neglected more than convalescence. The reasons are not difficult to find: when patients are deemed to be "recovered" we turn to new ill patients and leave the cured. But are they recovered? Are they fully cured? It is true that some are advised about convalescing and others sent to institutions giving convalescent care, but to assess the results of such care quantitatively and to assess the unsatisfied need for it is a difficult problem. Much is based on clinical observation and the tradition of "Send him to the seaside for a jolly good holiday." Is there any magic in sea air? It is most difficult for the investigator to find hard scientific facts and give an opinion. A survey[1] by King Edward's Hospital Fund for London should stimulate further inquiry, for, although this report deals in the main with what might be called the economics of the subject, many striking facts are brought to light from its study of 92 homes giving convalescent care, 19 London hospitals, and 2 provincial hospitals, over a six-months period in 1950. The Health Service does not really face the fact that it should be fully responsible for convalescence, and this has led to much administrative difficulty. When the State took over, only a minority of convalescent homes were included in the Health Service, and contractual arrangements have been made with the others for convalescent care. In the main there are two types of homes—convalescent homes taking patients from hospitals, and recuperative holiday homes taking patients from local health authorities—but the distinction is not clear-cut, which seems unsatisfactory, since it may lead to competition between both services for the available places. Some interesting figures lend point to this. Of over 4,000 hospital in-patients recommended for convalescence, 65.8% had to wait in hospital or at home for an average of 12¼ days. Those patients who spent this wait in hospital caused a loss of 11,140 hospital bed-days. For the corresponding out-patient figures 89.5% had to wait a minimum average time of 29 days. In the Fund's "summary observations and questions for further study" we find:

> If the staffing and equipment of a selected number of homes capable of providing nursing care were brought up to a higher standard it may well be that a number of such cases could be discharged from hospital earlier and so release hospital beds which are urgently needed;

and:

> We have noted that the provision of convalescence for children presents special problems and requires more careful and overall planning than it has yet received.

A comprehensive report, to be published, on the convalescent child has recently been completed in the Department of Child Health in the University of Liverpool, and this may throw light on the problems mentioned in the second quotation.

While all the questions presenting themselves to investigators have not been answered in the report, much information of value has been obtained, and we must note with gratitude that the King's Fund in the period 1947–50 expended £230,000 to aid convalescent homes.

[1] *Convalescence and Recuperative Holidays.* Published by King Edward's Hospital Fund for London, 10, Old Jewry, E.C.2. Pp. 45. 1s.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

CANCER OF THE SKIN

BY

HUGH GORDON, *M.C.*, M.B., F.R.C.P.

Physician-in-Charge of Skin Department, St. George's Hospital, London

Cancer generally is certainly not decreasing, and there is no reason to suppose that cancer of the skin is any exception to the general trend. Whilst undue prominence given to the subject of cancer in the lay press may lead to carcinophobia, it is probably in the interest of the patient that an accurate knowledge about skin cancer be made more widespread. On the whole, skin cancer is readily accessible to diagnosis and treatment. Furthermore, with one serious exception, it is relatively benign.

As the subject is a large one, only primary cancer of the skin is considered here, omitting secondary deposits from other organs.

Aetiology and Pre-cancerous Conditions

The final factor which determines that epithelial cells should take on abnormal proliferation and invade subjacent structures is uncertain or unknown. There are, however, a number of predisposing factors which recur in case histories and which antecede the appearance of skin cancer. These are trauma, naevi and other benign neoplasms, and certain skin conditions in which there has already been an epithelial change but as yet no invasion.

Trauma

Simple trauma is a common feature stressed by patients. "A blow on the face by a rhubarb stalk," "a nip on the nose by a crayfish," and "continuous squeezing of an exceptionally large blackhead" are actual examples. It is possible that patients are apt to overstress a remembered injury, as often enough there is a long period of quiescence. It is, however, undoubted that the long-continued traumatic effects of certain physical and chemical agents are predisposing in the production of skin cancer. These are sunlight, *x* rays, and tar.

Sunlight.—In the fair-haired (blond or red) with blue eyes and a tendency to freckle over-exposure to sunlight is undoubtedly an important factor. The most extreme instance is in the condition known as xeroderma pigmentosum, in which there is complete intolerance to sunlight. From earliest infancy even the slightest exposure is followed by intense freckling and the appearance of keratoses which are immediately followed by the appearance of carcinomata, generally of squamous type. When basal-cell or squamous-cell carcinomata are found in young adults, which is by no means uncommon, although the usual age is from 45 onwards, it is noteworthy that these patients are always blond with blue eyes and have been considerably exposed to the sun. It is well known that in Australia the incidence of skin cancer is considerably higher than in England, and again it occurs mostly in the fair-haired. In later life this type of subject gets numerous hypertrophic and pigmented areas on the face and the back of the hands; these finally form crusts—the so-called solar keratoses. Ulceration slowly occurs under these crusts and the ulcers become malignant, usually squamous-cell carcinomata. The condition is often known as "sailor's skin" (Fig. 1).

X Rays.—Chronic *x*-ray dermatitis or *x*-ray burn is practically always followed in due course by keratoses and subsequent carcinoma, usually squamous-celled in type. Examples occur after epilation by *x* rays—long since considered an unwise procedure—and after irradiation of secondary glands or other prophylactic procedures. It is a curious fact that usually the malignant

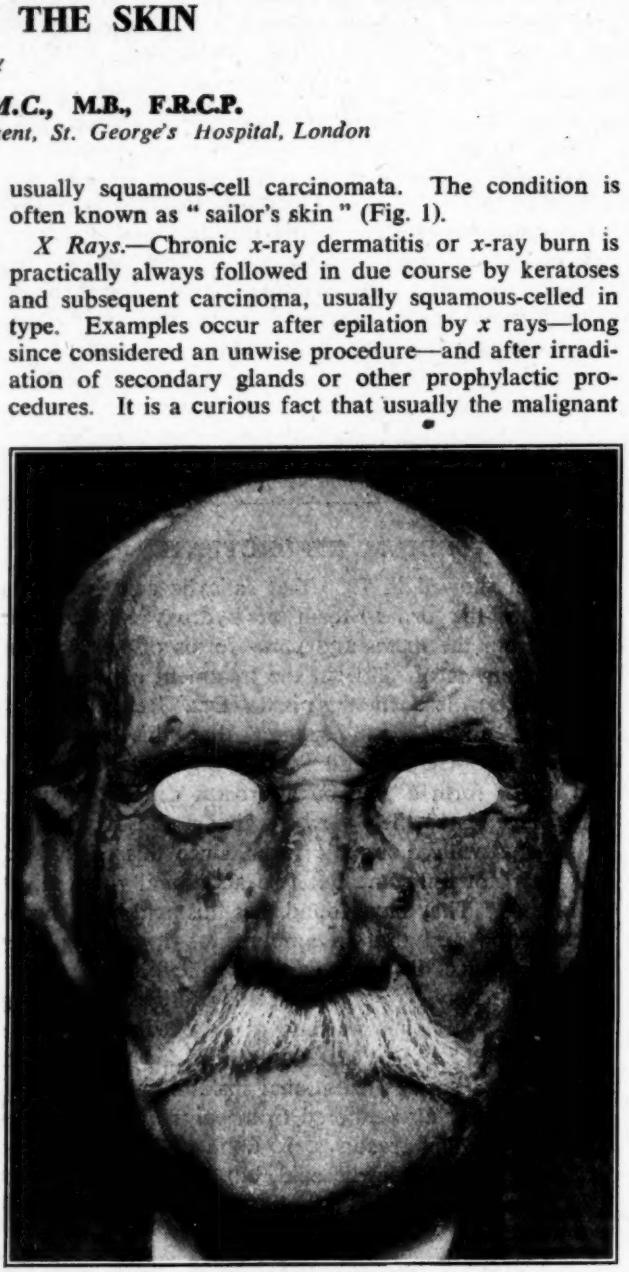


FIG. 1.—"Sailor's skin." Solar keratoses in a farmer. Early squamous-cell carcinoma on left cheek.

change does not occur for many years after the exposure Three to five years is the usual time lag, but periods up to twenty years have been noted.

Tar.—Exposure to pitch or tar is a well-known carcinogenic factor. All workers in gasworks are examined regularly at least twice a year. The earliest clinical appearance is a small wart, which may or may not change to a carcinoma, usually squamous-celled in type, within a matter of weeks. It is probable that an undue sensitivity to sunlight also plays a part in the production of these carcinomata, as many workers in the gasworks suffer regularly from what is known as "the smarts." This is an intense erythema of the face following quite ordinary exposure to sunlight.

Naevi and Other Benign New Growths

Naevi cells quite often take on malignant characteristics. It has been suggested that epithelial nests, though not producing a definite naevus, may precede the appearance of both basal-cell and squamous-cell carcinomata. This would be a satisfactory explanation for the cases of multiple rodent ulcers—up to fifty occurring in one person during the course of ten to fifteen years, and occasionally in several members of one family. It is possible to observe an ordinary non-pigmented naevus change insensibly, or after an infection, into a basal-cell carcinoma. Melanocarcinoma, which usually occurs on a pigmented naevus, is discussed below.

Virus warts are most exceptionally, if ever, followed by malignant change. This also applies in a lesser degree to the so-called seborrhoeic or senile warts—the greasy flat-topped warts so common on the temples and backs of the aged.

Senile keratosis is identical to solar keratosis, but occurs in the aged without any exposure to sun. It is pre-cancerous to the same degree.

Skin Conditions with Epithelial Change but no Invasion

Lupus vulgaris and psoriasis are quoted as preceding skin cancer. In both cases irradiation is often an important factor, particularly in lupus vulgaris, in which fairly large doses of *x* rays have often, but not necessarily always, been given. It is doubtful if unirradiated psoriasis ever produces a malignant change.

There is a group of definite pre-cancerous skin conditions, comprising Bowen's disease, Paget's disease of the nipple, and Queyrat's erythroplasia of the penis, in which the cancerous changes are entirely intra-epidermal. The history of these cases is lengthy, varying from five to fifteen years, before they develop into true squamous-cell carcinomata.

Leucoplakia of the mouth, tongue, and vulva is also a true pre-cancerous condition, although here the history is much shorter before the advent of malignant change.

Basal-cell Carcinoma and Squamous-cell Carcinoma

These comprise the vast majority of skin cancers. A rough estimate would be that basal-cell carcinomata are ten times more frequent. They have a striking predilection for the face, particularly in the area bounded by lines drawn from the angle of the eye to the tip of the ear and from the corner of the mouth to the angle of the jaw. The scalp is a not uncommon site, whilst the body is relatively untouched except by the multiple superficial variety.

FIG. 2.—Typical basal-cell carcinoma with well-marked pearly edge.

Squamous-cell carcinomata are also often found on the face, but, as they more frequently follow trauma of all sorts, they are more common than basal-cell carcinomata on the hands, arms, legs, and scrotum.

Clinical Description.—The chief characteristic of a basal-cell carcinoma is a hard rolled edge of cartilaginous consistence and pearly colour (Fig. 2). This is always present to some degree, but is sometimes obscured by other features. It is very commonly crossed by telangiectases. Central ulceration varies from a dimple to a deep excavated ulcer. The rate of growth is slow, many lesions remaining unchanged over years, and the average history given by the patient varies from one to ten years. In a squamous-cell carcinoma the original formation is papular. There is no specific hard edge, but a surrounding induration and slight inflammation are present. A central embedded keratosis is a feature which slowly gives way to a ragged central ulceration.

Malignancy.—Basal-cell carcinomata are only locally malignant, destroying adjacent tissue by geographical spread. This can destroy bone and cartilage, and large areas are often involved, particularly when the lesion has penetrated at the angles of the nose or ear or on the surface of the scalp. Metastases, on the other hand, do not occur. Squamous-cell carcinomata produce metastases but relatively slowly, the favourite sites being the ear and scrotum. Metastases occur very much earlier and more frequently when the growth involves the mucous membrane, such as the lip or vulva.

Differential Diagnosis.—This is set out in the table. For purposes of description basal-cell carcinoma is considered under five headings. It must be emphasized, however, that these overlap to some extent, and that their strict differentiation is rather didactic.

Type of Basal cell Carcinoma	Common Site	Clinical Features	Differential Diagnosis
1. Ulcerating	Angles of nose, eye, and ear	Edge obscured by scab and ulcerating; depth of ulcer greater than width of lesion	Squamous-cell carcinoma
2. Button ..	Cheeks	All hard edge; central depression; average width 1.5 cm.	Naevus; squamous-cell carcinoma
3. Cystic ..	Nose	Cartilaginous edge slight; body cystic; scabs and ulceration rare; average width 1·5 cm.	Sebaceous and other cysts; pyogenic granuloma
4. Scarring	Temples, scalp, and neck	Peripheral spread greatest; cartilaginous edge slight; centre covered with crust which covers superficial erosion and healed scarring; average width 5 cm.	Lupus vulgaris; tertiary syphilide
5. Multiple Superficial	Body	Same characteristics as scarring, only all features diminished; scarring invisible; cartilaginous edge only apparent with lens as slightly raised border; scabbing very slight; average width 1–3 cm.	Psoriasis; eczema

Melanocarcinoma

Basal-cell and squamous-cell carcinomata are both relatively benign, and, although tragic cases occur in which bones are affected in the case of basal-cell carcinomata or secondaries are allowed to develop in the case of squamous-cell carcinomata, these are usually due to neglect or a late diagnosis. Occasionally, however, even in the most expert hands a basal-cell carcinoma will recur and give rise to serious mutilation and a doubtful outcome. In squamous-cell carcinoma the possibility of metastases must always be considered, and follow-up is essential at three-month intervals for the

first year. If, however, metastases do occur they can usually be dealt with successfully by surgery or radiotherapy if diagnosed early.

The picture is totally different with melanocarcinoma. It is black in every sense of the word. This extremely malignant condition arises from a naevus. Any naevus is a candidate for malignant change, either pigmented or unpigmented. In over 90% of the cases, however, the primary lesion is a blue-black or black, smooth, non-hairy naevus. Probably one person in ten has such a naevus somewhere on his skin, and in view of the comparative rarity of the disease the chance of any one naevus becoming malignant is therefore a very long one.

Clinical Picture.—The average story is as follows: The patient has been aware of the presence of a black

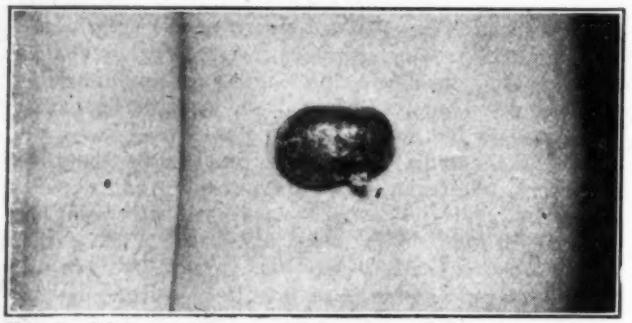


FIG. 3.—Melanocarcinoma of arm. Increase in size noted for three months.

naevus for a number of years, or possibly for life. During, however, the last two to six months it has gradually increased in size or deepened in colour. More recently it has become a little lumpy and the surface has tended to break or to bleed, with the appearance of superficial scabs. The next feature is generally definite induration of the base and possibly some inflammation or the appearance of a small black satellite naevus in the immediate vicinity. At this stage it may be highly malignant. Metastatic melanocarcinoma cells will be found in the surrounding lymphatics and in the draining lymphatic glands. Spread is also blood-borne (Fig. 3).

Differential Diagnosis. — There are several conditions in which pigmented papular lesions give rise to alarm in the circumspect doctor. The two most important are:

Seborrhoeic Wart.—Patients are constantly being referred on account of a blackish lesion on the skin which is increasing in size. If the lesion happens, as is usual, to be a single one the alarm is understandable. Frequently, however, quite a number of similar lesions are found scattered over the trunk, but one particular lesion has increased in size and is predominant. Even so, the slightly greasy corrugated scale is typical. There is no induration, and the pigment is not true melanin and does not impregnate the skin.

Pigmented Basal-cell Carcinoma. — All moles, pigmented and otherwise, occasionally swell and discharge. This is due to an ordinary staphylococcal infection of the underlying sebaceous gland or hair follicle. Again, a pigmented mole, not necessarily blue-black or black, may change clearly in appearance and become indurated. Within the course of months or years it becomes obvious that it is a basal-cell carcinoma arising on a mole. If such a lesion is treated by radiotherapy the basal-cell carcinoma disappears completely and leaves a pigmented mole.

Treatment of Skin Cancers

With rodent ulcers biopsy is always desirable because it clinches the diagnosis, although in many cases the clinical picture is so definite that, given reasonable experience, a biopsy may not be necessary for this purpose. Occasionally, however, a mixed basal-cell and squamous-cell lesion is found when not expected. This does not materially alter the method of treatment to be selected, but on account of possible metastases it does alter the importance of the follow-up.

In suspected squamous-cell carcinomata the diagnosis is seldom so obvious and a biopsy is essential.

In suspected melanocarcinomata a biopsy is strictly contraindicated, as any traumatic procedure, short of wide and deep excision, increases the risk of dissemination.

When carrying out a biopsy in small lesions the practicability of surgical removal obviously needs consideration in order to avoid having two bites at the cherry.

General Considerations

The primary aim of treatment is always the same—that is, the complete extirpation of all pre-malignant or malignant cells in the primary lesion and of the draining glands if they are involved. It is of great importance that this should be performed in one and the first procedure, as recurrences in the primary lesion tend to get progressively and rapidly more recalcitrant to treatment.

There are secondary considerations in treatment which concern the patient more directly. These are: (1) expense, which includes the time involved in treatment; (2) discomfort and reaction during treatment; (3) the cosmetic appearance of the cured lesion; and (4) the achievement of a sound scar which will not break down later.

The standard methods of treatment are surgery and radiotherapy. They are not necessarily alternatives, but

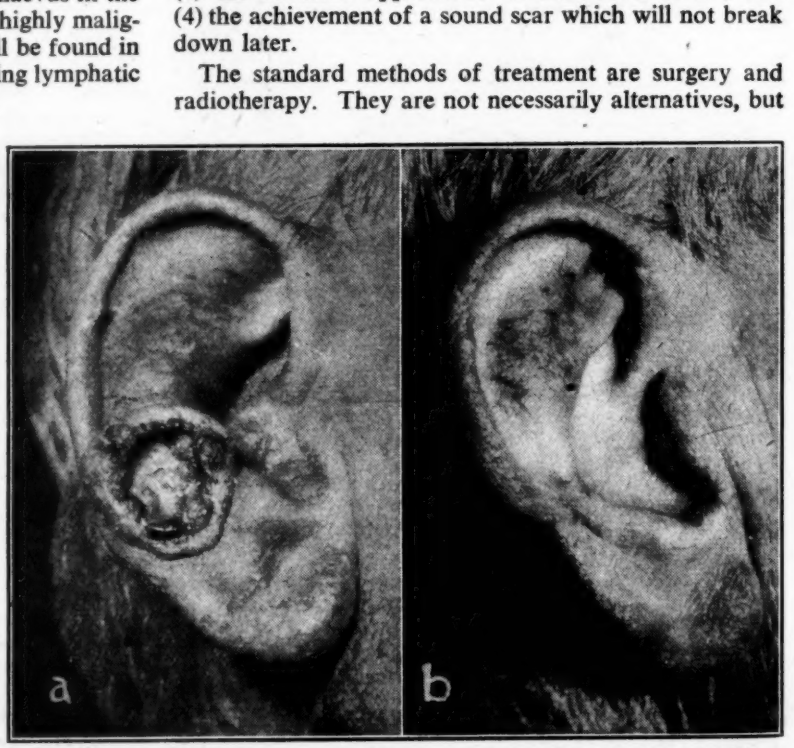


FIG. 4.—Squamous-cell carcinoma of right ear of two months' duration. *a*, Before treatment. *b*, After radiotherapy.

should be complementary. Unfortunately, perhaps, each expert involved is apt to expatiate on the advantages of the method in which he is primarily interested and with which he is familiar. When skin cancers are considered by a team it will be found that the method of choice largely depends on the site, size, and other factors in the lesion under review. Success depends more on the skill with which surgery or radiotherapy is employed than on the exclusive choice of one of the two methods.

Surgery

To be effective this necessitates a wide and deep excision, for depth recurrence is nearly as frequent as edge recurrence. The great advantage of surgery in small lesions is that only one sitting is required, with a subsequent reattendance for the removal of stitches. Its disadvantage is that so many rodent ulcers occur at awkward sites, such as the angles of the nose and eyes, and that a sufficiently wide excision necessitates quite extensive grafting. In lesions of the ear and lip particularly, the cosmetic result of excision and grafting does not compare with that of radiotherapy (Fig. 4).

Surgery is without question the method of choice when cartilage and bone are involved, and in melanocarcinomata, which are practically always radio-resistant. The surgical procedure in melanocarcinoma must be drastic. R. W. Raven recommends an incision at least 5 cm. from the primary lesion and removal of the fascia 10 cm. away from the edge of the tumour, which must not be touched by scalpel or forceps during the operation. Radical excision of the regional lymph nodes must be performed in every case of melanocarcinoma.

Radiotherapy

This includes a wide range of methods, including *x* rays of short to long wavelengths and radium used as a plaque (beta rays) or as applicators and implants (gamma rays). The details of radiotherapeutic treatment are outside the scope of this article. Many variants of available techniques give equally good results in expert hands. The chief advantage of radiotherapy is that it does not necessitate loss of tissue, owing to the selective action of irradiation on cancer cells. Consequently scarring is minimal. It has the disadvantage of requiring a necessary period of reaction, which starts about ten days after completion of treatment and may last up to a month. During this time the lesion discharges and forms repeated scabs which may become secondarily infected. The normal irradiated skin surrounding the lesion proceeds to an erythematous reaction which may for a few days be moist.

Suitable applications during the reaction are:

Calamine *B.P.C.*	1 dr. (4 g.)
Zinc oxide	½ dr. (2 g.)
Glycerin	½ fl. dr. (1.75 ml.)
Spirits of camphor	½ fl. dr. (1.75 ml.)
Distilled water	1 fl. oz. (28.4 ml.)

or

Zinc peroxide	1 dr. (4 g.)
Zinc oxide	4 dr. (16 g.)
Lanolin	2 dr. (8 g.)
Lime water	1 fl. dr. (3.5 ml.)
Olive oil	1 fl. oz. (28.4 ml.)
Colouring matter	q.s.

The treated lesion heals more quickly if not covered with a dressing except for the shortest periods, which may be necessary for cosmetic reasons. It must be remembered that treated lesions should be regarded with more respect than normal skin, and should not be subjected to trauma or extreme exposure to sunlight.

Research still continues in order to find the optimum dosage and method of treatment.

Correction.—Dr. Gilbert Forbes writes: "In my article 'Blood Groups and Disputed Paternity' (July 28, p. 227) the first sentence of the section *Source of Antisera* should read, 'As group A blood serum naturally has the antibody β (anti-B), and group B blood serum naturally contains the antibody α (anti-A) . . .'"

CONFERENCE ON INFECTIOUS DISEASES

The first British–Danish Conference on Infectious Diseases was held in Copenhagen during the week July 2 to 6. Although the meetings were of an informal character, arranged mutually by Professor H. C. A. LASSEN, of Copenhagen, and Dr. T. ANDERSON, of Glasgow, much original work was reported and a valuable exchange of views took place on problems common to the infectious diseases in both countries.

Anterior Poliomyelitis

At the first session, with Dr. T. ANDERSON in the chair, Dr. IAN B. L. WEIR (Glasgow) gave an account of the epidemiology of this infection in the City of Glasgow. On three occasions in the last 25 years the attack rate had exceeded 100 per million—in 1928 (101), 1947 (297), and in 1950 (255). The last two epidemics had many contrasting features, which are shown below:

	1947	1950
Case rate per million	297	255
Main period of epidemic	July–Sept.	April–Oct.
Peak notifications per week	70	30
Proportion in 0–4 age group	53%	73%
Respirator cases	24	12
Mortality rate	12%	4%

A curious feature which required further study was that, in both epidemics, an excess of bulbar cases had been observed among persons whose tonsils had been removed at some time in their lives. A follow-up study in 1951 of the 1947 cases had shown that, of 72 in which the paralysis had been severe, 20 had made an excellent recovery; of 88 in which paralysis had been moderate, 62 had recovered completely; and all of those in which the paralysis had been originally minimal (48) were now free from any disabling effect. Thirty children required to attend special schools and four were still in the orthopaedic hospital.

Prognosis of the Paralytic Case

Professor H. C. A. LASSEN (Copenhagen) had studied the early and late prognosis of the cases seen at Blegdams Hospital during the 1944 epidemic. Particular attention had been paid to the early progression of the paralysis. It was found that in 83% of the paralysed cases the paresis had started within five days of the onset of illness. In about half of the patients further progress of the paralysis ceased within 24 hours of its inception, and in only 14% did paralysis continue to progress for more than 72 hours. Although prolongation of fever was usually an excellent guide to the possible extension of paralysis, in 5% of the paralysed patients there was further involvement after fever had ceased; and a similar proportion which showed no paralysis while febrile went on to develop paralysis after the temperature had become normal. Muscle recovery had

been carefully assessed in a follow-up study three and a half years later. In 50% there was normal working capacity, and a further 25% were able to earn their living despite remnants of paralysis. Only two patients remained permanently disabled. A considerable difference had been observed in the regenerative capacity of different muscle groups. Thus, the opponens pollicis, the abdominal muscles, and the small muscles of the foot showed the worst prognosis. No explanation for this difference between muscles could be advanced.

Bulbar Poliomyelitis

Dr. P. MCKENZIE (Glasgow) analysed some of the clinical features of the bulbar cases seen in 1947 and 1950. Out of the 208 cases admitted to Belvidere Hospital, 41 were classified as bulbar or bulbo-spinal. Of these, 20 were in the upper cranial nerve group, 7 in the lower cranial nerve group, and 14 involved the cardio-respiratory centre with or without involvement of arms or legs. Practically all of the deaths occurred in the last group. It was interesting that, although only 2 out of 27 cases with cranial nerve involvement had shown extension downwards to the cardio-respiratory centre, 8 out of 51 with arm or shoulder-girdle paralysis had spread upwards. The graver prognosis in the older age groups was shown by the fact that the fatality rate in those under 15 years was 4% compared with a rate of 27% in those over this age.

Post-inoculation poliomyelitis was dealt with by Dr. H. S. BANKS (London), who reviewed recent information on this subject, much of it from personal communications from workers in different parts of the world. He concluded that injections increased the risk of acquiring paralytic poliomyelitis, particularly in the age group 0–5 years. Dr. W. GUNN (London) discussed the use of mechanical respirators and gave a description of one which had been made to his own design.

Pertussis

At this session the chair was taken by Dr. THORVALD MADSEN (Copenhagen).

Clinical Trials of Chloramphenicol

Dr. T. ANDERSON (Glasgow) and Dr. E. C. BENN (Leeds) gave an account of the preliminary analysis of the results in the trial of chloramphenicol and aureomycin in pertussis; this trial had been carried out in Great Britain under the auspices of the Medical Research Council, but the results were not yet available for publication.

Professor H. C. A. LASSEN and Dr. L. C. GRANDJEAN (Copenhagen) had treated 100 consecutive cases of pertussis with chloramphenicol. The antibiotic was given per rectum to children under 6 years and by mouth over this age. *H. pertussis* disappeared from the posterior pharynx within two days in 73 patients and remained absent until four days after treatment had ended. The return of organisms to the nasopharynx was observed in a number of cases, but could not be ascribed to the development of resistant strains of *H. pertussis*. It seemed possible that ward reinfection played a part, for, of 41 patients treated in isolation, only 2 had shown persistence of the organism after stopping treatment. The clinical results were considered excellent, no matter at what stage of the disease the treatment was started. These papers gave rise to considerable discussion, and it was apparent that there was no unanimity of opinion on the value of chloramphenicol in whooping-cough. Dr. W. JAMIESON (Dundee) thought that the dosage used in many centres in Great Britain was on the small side, and felt that the larger dosage used in Denmark (which was similar to that used by him) was an explanation of the divergence.

Dr. H. S. BANKS (London) described the use of a decompression chamber in the late treatment of pertussis. Four hundred and sixty-five cases had now been treated at the Park Hospital, with considerable improvement in 269 (57%). Although he made no strong claim for this method of treatment, he felt the results justified a more extended trial, especially in cases in which distressing spasms of coughing continued into convalescence.

Parapertussis

Dr. H. LAUTROP (State Serum Institute, Copenhagen) analysed a series of 171 patients from whom *H. parapertussis* had been isolated. Although a comparison of the illnesses produced by this organism and by *H. pertussis* had shown a similar symptom-pattern, parapertussis was in every respect a much milder illness. In many cases the symptoms were so mild that whooping-cough would not have been suspected, and, in contrast to whooping-cough (where the isolation of the organism from persons without clinical evidence of the disease was rare), *H. parapertussis* had been isolated from nine persons who were free of symptoms of any disease. There was some evidence, too, of reciprocal immunity. In 25 patients with parapertussis who had a history of previous whooping-cough, the disease took a particularly mild course. On the other hand, a previous attack of parapertussis did not seem to lessen the severity of a subsequent attack of pertussis. He considered that both organisms produced the same toxin, but that *H. pertussis* produced it in much greater quantity, and that the organisms had different surface antigens.

Gastro-enteritis

The third session was held at the State Serum Institute through the courtesy of Dr. F. ORSKOV and was attended by many of the workers there, including Dr. F. KAUFFMANN.

Pathogenic Strains of Bact. coli

Dr. JOAN TAYLOR (London) gave an account of the close epidemiological association between certain types of *Bact. coli* (O111, B4; and O55, B5, H6) and outbreaks of infantile diarrhoea and vomiting in different parts of England. She also described the work done by Dr. K. B. Rogers (Birmingham), who had studied the spread of these two types of *Bact. coli* among children in paediatric units. Infants with gastro-enteritis associated with these type strains often excreted large numbers of coliforms. Heavy contamination of the air and all ward furnishings associated with the patient quickly occurred and resulted in a very high rate of hospital cross-infection.

Dr. A. DUPONT (State Serum Institute, Copenhagen) had examined faecal specimens from 3,104 infants under 1 year of age during the period April, 1950, to April, 1951, and had found that *Bact. coli* O55, B5, H6 was closely associated with outbreaks of diarrhoea. With one single exception, she had been unable to isolate such strains from 3,168 faecal samples obtained from healthy newborn infants, healthy children under 1 year of age, and children with non-diarrhoeal diseases. The isolation of yet another specific strain of *Bact. coli* (O55, 26) from a group of infants with diarrhoea was reported by Dr. FRITS ORSKOV (Copenhagen). This strain had also been isolated in Finland and England.

Viral and Nutritional Factors

Dr. B. P. MARMION (London) described investigations on the possible aetiological role of a virus in the neonatal and "mother–child" types of gastro-enteritis. The nutritional approach to infantile gastro-enteritis was considered by Dr. N. R. GRIST (Glasgow), who found evidence of hepatic damage at necropsy in 20 out of 30 fatalities occurring in a series of 230 cases of gastro-enteritis. He suggested that the frequent association of hypoproteinaemia and signs of liver damage during the acute illness might result from the starvation caused both by the disease itself and by the usual methods of early treatment. Dr. C. ROSS (Glasgow) reported a study of excretion of amino-acids in the faeces of healthy infants. In the breast-fed infant the faecal amino-acid excretion differed quantitatively and qualitatively from that found in the infant receiving artificial feeds. It was suggested that certain environmental conditions in the

intestine of infants might be intimately related to the establishment of potential pathogenic organisms and might explain the greater incidence of gastro-enteritis in artificially fed infants.

Pneumonia

At the fourth session Dr. H. S. BANKS (London) occupied the chair.

Therapeutic Trials in Bacterial Pneumonias

Dr. A. DRIMMIE and Dr. T. ANDERSON (Glasgow) gave a preliminary analysis of the results of the therapeutic trial of aureomycin and chloramphenicol in adult pneumonia. This trial had been carried out in four centres in Britain under the auspices of the Medical Research Council, but the results were not yet available for publication.

Dr. J. B. LANDSMAN (Glasgow) analysed the results of treatment of 312 cases of adult bacterial pneumonia with different forms of chemotherapy. The methods of treatment were allocated by random selection, and the numbers of cases were as follows: intramuscular penicillin, 101 ; oral penicillin only, 109 ; a single injection of penicillin intramuscularly followed by oral administration, 32 ; combined sulphonamide and oral penicillin, 30 ; and aureomycin orally, 40. The different groups were roughly similar in regard to the usual prognostic factors. The results in those who received oral therapy with penicillin only had not been so good as those in the other treatment groups, and it was felt that the initial treatment should not be by this route.

Dr. A. CHRISTENSEN, Dr. B. KORNER, and Professor H. C. A. LASSEN (Copenhagen) gave an account of 68 patients with pneumonia treated with "leocillin" (benzyl penicillin β-diethyl-aminoethylester hydriodide). Preliminary experiments by K. A. Jensen and others had suggested that its ability to penetrate membranes and accumulate in various organs—for example, the lungs—might give it a special sphere of usefulness in the treatment of lung infections. The substance was given parenterally to 32 patients in a daily dose of 300,000 units for five to six days. The result was excellent in 20 out of 26 uncomplicated cases, of which two failed to respond. In six patients whose pneumonia was complicated by a pre-existing chronic bronchitis the effect was good, but the patients ran a somewhat prolonged low-grade fever. Thirty-six patients were treated orally with a single large dose of 1,000,000 units. Although the results were again good in the majority of the patients, two failed to respond, and in a further ten there was a secondary rise in temperature associated with relapse.

Non-bacterial Pneumonias

An account of the British experience in regard to non-bacterial pneumonic infections was given by Dr. B. P. MARMION, Dr. A. D. MACRAE, and Dr. N. R. GRIST (London and Glasgow). Dr. Marmion described how 80 cases of Q fever had been encountered in Great Britain during the past two years. Although it had not yet been possible to make a complete survey of the country, present results indicated that the disease existed in local foci corresponding broadly to those areas where cattle-breeding and milk production predominated. Dr. Macrae had obtained serological evidence of infection by the psittacosis group of viruses in a small proportion of specimens submitted to the Virus Reference Laboratory (of the Public Health Laboratory Service) from "atypical" cases of pneumonia. Dr. Grist recorded the examination of paired sera from 341 consecutive admissions to wards receiving cases notified as "pneumonia." Evidence of virus infection was found in 27%, the bulk of these occurring during the 1951 influenza epidemic. Only two patients had shown significant levels of cold agglutinins, and one case of ornithosis was detected. During the influenza epidemic of the winter of 1950–1 in Glasgow there had been a close parallelism between the curves for serologically positive influenza infections, the weekly notifications of pneumonia, and the deaths from respiratory disease.

Acute Disseminated Tuberculosis

At the final session Professor H. C. A. LASSEN took the chair.

Dr. P. MCKENZIE (Glasgow) analysed a series of 528 cases of tuberculous meningitis collected from the fever hospitals of Glasgow (311), London (67), and Dublin (150). The interesting finding emerged that the recovery rate was best in London (58%), intermediate in Glasgow (44%), and worst in Dublin (27%). Although the schemes of treatment had varied in the different centres, all cases had received adequate intramuscular and intrathecal therapy. There were certain differences between the clinical characteristics in the three cities. Thus in London and Dublin about one-quarter of the cases occurred during the first three years of life, whereas in Glasgow one-third of the cases were in this age group. It was also interesting to find that in London one-third, in Glasgow one-sixth, and in Dublin one-sixteenth of the cases were admitted in what was regarded as an early stage of the illness. No doubt allowance had to be made for individual variations in classification, but these differences were striking and ran parallel to the differences in fatality rates. All but 26 of the 216 survivors had been under observation for more than one year since starting treatment. Dr. McKenzie wondered whether race might have some significance, in view of the fact that the figures for Dublin and Glasgow differed so much from those for London. Was it possible that the common Celtic stock in the former cities played an important part ?

Professor H. C. A. LASSEN and Dr. F. NEUKIRCH (Copenhagen) analysed the results of treatment of 50 patients with streptomycin. Of these, 6 had miliary disease of the lungs alone, 32 had tuberculous meningitis, and 12 had tuberculous meningitis and miliary pulmonary tuberculosis. The observation period was from 21 to 43 months. Of the 32 meningitis cases, 20 were treated solely by the intramuscular route and 7 recovered ; 12 were given combined intrathecal and intramuscular therapy and 4 recovered. The Danish experience suggested that intramuscular therapy alone achieved results as good as those with combined therapy. Further, none of these patients had developed deafness, and the opinion was expressed that intrathecal therapy might increase the risk of deafness, perhaps especially when dihydrostreptomycin was used intrathecally.

Effect of Streptokinase in Tuberculous Meningitis

Dr. M. B. EADIE (Glasgow) recorded the results in a group of 38 cases of tuberculous meningitis, of which 17 had been given a uniform daily dose of streptokinase (6 units) intrathecally, in addition to combined intramuscular and intrathecal streptomycin. The fatality rate for the series as a whole had been 66%, and streptokinase did not seem to have exerted any marked effect either upon mortality or on the occurrence of complications. The routine scheme of treatment in the hospital had been to give the initial daily intrathecal injections in two courses of 21 days separated by an interval of one week. Many patients had exhibited severe reactions when the second course of streptokinase injections was instituted. These reactions produced alarming clinical signs as well as marked changes in the cerebrospinal fluid. Since it was thought that these reactions were of the nature of a sensitization, and since some of the patients in whom they occurred had appeared to benefit, a more recent series of cases had been given gradually increasing doses of streptokinase during the first course of intrathecal injections. These had produced marked changes in the cerebrospinal fluid, and, although the period of observation was too short for a definitive statement, seven out of the nine patients so treated were alive and making excellent progress.

Danish Arguments Against Intrathecal Streptomycin

Dr. T. HILDEN and Dr. B. MØLLER (Copenhagen) described experiments in which the concentration of streptomycin in the cisternal cerebrospinal fluid was determined after injection by the usual lumbar route. In the early stage

of intrathecal therapy a marked rise in the concentration in the cistern was observed one to two hours after lumbar injection. But in the majority of patients who were in the later stages of treatment a rise in the cisternal concentration was not noted. There was also evidence to suggest that even in the early cases the rise in the cisternal level was not of long duration. These results suggested the possibility that lumbar injection of streptomycin might induce arachnoiditis which later interfered with the upward passage of streptomycin, and added point to the Danish contention that intrathecal therapy through the usual lumbar route might not achieve what was intended—namely, consistently high levels at the base of the brain.

Prognosis in Miliary Tuberculosis

Dr. J. H. LAWSON (Glasgow) analysed a collected series of 39 cases of miliary tuberculosis in which meningitis was not present when streptomycin therapy was begun. As with meningitis, age seemed of importance in prognosis, for 8 of the 11 deaths had occurred in the youngest and oldest age groups. Thirteen of the patients developed meningitis while undergoing treatment. The average period between commencement of treatment and development of meningitis had been 10 weeks; but five had developed it during the first four weeks and eight between the 12th and 24th weeks. There was a remarkable similarity between the different age groups in the length of time elapsing before the "snow-storm" appearance in the radiograph disappeared—namely, 18 weeks. The tuberculous meningitis when it appeared seemed still susceptible to therapy, for 7 of the 13 cases had recovered. The other five deaths resulted from extensive tuberculous dissemination.

These papers gave rise to a very lively discussion.

B.C.G. Vaccination

Dr. WINGE, Dr. TØRNING, and Dr. K. JENSEN (Copenhagen) all referred to the benefits arising from the use of B.C.G. vaccination in Denmark. It was now estimated that between 120,000 and 140,000 persons in Copenhagen had been vaccinated out of a population of less than 1,000,000. Since 1936 no case of tuberculous meningitis had been observed in a person successfully converted by B.C.G. vaccination. Professor LASSEN reported that for many years in Blegdams Hospital beds had been set aside for cases of primary tuberculosis. In 1949 there were 72 such beds, in 1950 54, and in 1951 18. At the present time only 10 of these beds were occupied.

Dr. WEIR showed that in Glasgow the statistics for deaths from tuberculous meningitis had changed markedly in recent years. It was clear, however, that the reduction in mortality was most marked in the 5–24-years age groups and that one-half of the deaths now occurred in the first three years of life. Some form of immunization which would spare attack at this dangerous age seemed the only way in which the statistics could be improved.

Conclusion of the Conference

In concluding the conference, Professor LASSEN thanked all those who, by contributing papers, had helped to produce a notable conference. It was clear that Danish and British methods for the control and treatment of infectious diseases had much in common: where differences existed, each country could learn from the other, especially from such informal discussions. Dr. ANDERSON, on behalf of the British delegates, thanked their Danish hosts for accepting the idea of the conference with such enthusiasm and for the wealth of hospitality which they had showered on their alien guests.

Spring cleaning caused 7% of the accidents reported in one day to the Edinburgh Accident Prevention Council (*Scotsman*, July 3). In many other cases children had swallowed medicines left within their reach. Razor blades, also, were responsible for a number of accidents in the home.

INTERNATIONAL CONGRESS OF CLINICAL PATHOLOGY

The first International Congress of Clinical Pathology was held in London from July 16 to 20. An account of the official receptions given in connexion with the Congress, and reports of the proceedings of the Sections of Microbiology, Haematology, and Chemical Pathology, were printed in our last issue (August 4, p. 290). This week we report the proceedings of the Section of Histopathology, and give an account of the two joint sessions.

IV. SECTION OF HISTOPATHOLOGY

Effects of Irradiation on Tumours

Professor J. H. DIBLE was chairman of the first half of the opening session and Dr. R. J. LUDFORD of the second.

Dr. R. J. LUDFORD (London) described some of the effects of irradiation on experimental tumours—the inhibition of mitoses, production of mitotic anomalies, differentiation of tumour cells, and damage to blood vessels. He put forward the view that secretion or keratinization in certain tumours after irradiation might be a direct consequence of the inhibition of their division. Dr. P. C. KOLLER (London) briefly reviewed the morphology of radiation-induced injury to tumour cells, and went on to stress the role of the tumour bed—vessels, stroma, lymphocytes, and reticulo-endothelial cells—in helping to destroy the tumours. In the discussion Dr. LUDFORD maintained that no convincing evidence of the existence of a defence mechanism against cancer had ever been demonstrated. Professor H. HAMPERL (Marburg) suggested that cell differentiation might be a direct result of irradiation and the inhibition of mitosis a resultant secondary effect.

Dr. A. GLUCKSMANN (Cambridge) demonstrated differentiation in irradiated normal human stratified epithelium, and showed examples of response to irradiation in squamous-cell carcinoma by cornification, sarcoma by fibre formation, and osteosarcoma by bone formation. He considered that the differentiation might result partly from mitotic inhibition and partly from a direct effect of the irradiation. Dr. C. W. TAYLOR (Birmingham) showed in a series of treated carcinomas of the cervix that it was possible for the pathologist to make an assessment of response to radiotherapy by critical comparison of satisfactory pre- and post-irradiation biopsies. Dr. CORA P. CHERRY (Cambridge) demonstrated irradiation effects on a series of adenocarcinomas of the cervix, and Dr. GEORGE LUMB (London) on 80 cases of carcinoma of the breast.

Dr. P. R. REZEK (Miami) had observed squamous-cell metaplasia in areas within carcinomas of the prostate and their metastases in bone in cases treated both with and without oestrogen. A similar change was seen in non-cancerous prostates, especially in cases of liver disease. In the discussion Professor R. A. MOORE (St. Louis) suggested that the oestrogen-induced squamous metaplasia seen in prostatic carcinoma might represent a duct origin of the growth and its absence be suggestive of an acinar origin.

Collagen Diseases and Other Disorders of Extracellular Material

The chair at this session was taken by Dr. W. A. D. ANDERSON (Milwaukee) and Dr. F. LINELL (Lund) successively. It was much regretted that Professor P. KLEMPERER (New York) was unable to give his opening paper.

Dr. G. TEILUM (Copenhagen) put forward his views on the antagonism between ascorbic acid and cortisone in mesenchymal reactions—a morphological counterpart in some respects to Selye's adaptation syndrome. Teilum had found that in animals treated with casein which had not developed amyloidosis exposure to cortisone induced a prompt and massive amyloidosis which could be inhibited by ascorbic acid. He suggested that the normal mesenchymal response

to a noxious stimulus was a proliferation of modified lymphocytes (pyrinophil cells) and plasma cells with a gamma-globulin increase; this then merged into the stage of healing or hyalinization, but there might be an abnormal phase, such as was seen in rheumatoid arthritis, due to disturbance of tissue enzymes, and perhaps to excess production of adrenocortical hormones, so that there was a formation of amyloid, associated with abnormal plasma proteins, instead of the formation of collagen.

Dr. CONRAD PIRANI (Chicago) had made somewhat similar observations from a slightly different angle in that he had found that amyloidosis developed in subscorbutic animals. He suggested that as a consequence of the ascorbic acid deficiency there was a depolymerization of ground substance, with an elevation of serum glycoproteins. If this persisted long enough, the abnormal glycoproteins would precipitate as amyloid.

Dr. J. A. MILNE (Glasgow) gave a further report (see *British Medical Journal*, 1951, **1**, 383) on the remarkable improvement induced in scleroderma by the exhibition of 3-hydroxy-2-phenylcinchoninic acid; it would seem that these changes were quite distinct from a cortisone effect and were more probably associated with a modification and dissolution of the hyalinized tissue.

A paper by Dr. L. E. GLYNN and his co-workers (Taplow) described their studies on fibrinoid, using both histo-enzymic analysis and classical biochemical methods. They had shown that fibrinoid was quite distinct from fibrin, and that fibrinoid was in all probability an abnormal collagen impregnated with a mucopolysaccharide. Dr. J. BALL (Manchester) and his colleagues (Leeds) had gone a stage further in the study of fibrinoid, and had used *x*-ray analysis to study the molecular pattern of known areas in a section examined by a light microscope in which certain of these areas had been subjected to electron microscopy. This very elegant technique enabled him to show that there was almost certainly a high polysaccharide content in fibrinoid and that the collagen was abnormal; in advanced fibrinoid change these were replaced by non-fibrous membranes which were resistant to trypsin.

However, the whole morning was not devoted to the realm of ultrastructure, and Drs. L. DESCLIN and W. GEPTS (Brussels) described a group of cases in which they had observed intimal proliferation with acute fibrinoid change in the small vessels—the type of lesion which Rössle had called "rheumatoid"; these changes had chiefly been seen in cases of pulmonary arterial fibrosis, but one case had also shown lesions in hepatic veins approaching those found in Chiari's syndrome. It was suggested that the pulmonary vascular lesions were not to be regarded as local phenomena, but rather as part of a generalized vascular dysplasia.

Physical Methods in Histopathology

Professor R. A. MOORE (St. Louis) was in the chair at this session.

Dr. C. WOLPERS (Lübeck) described the value of electron-microscopy in the study of collagen, and demonstrated the fundamental breakdown of the fibres infected with myxoma virus. Dr. G. LELLI (Rome) showed that the intimate structure of the normal collagen fibres was revealed by treatment with trypsin. Dr. R. REED and Professor W. T. ASTBURY (Leeds) had studied normal and abnormal skins, and stated that the elastica of ordinary microscopy, as seen in senile elastosis and pseudoxanthoma elasticum, was by electron microscopy shown to be not elastica. Dr. R. BARER (Oxford) ended this symposium by describing phase-contrast, interference, and reflecting microscopes.

Dr. G. BRANTE (Gothenburg) discussed the deposits in gargoylism, which he described as lipoidal gangliosides and water-soluble polysaccharide esters. Dr. G. CRAWFORD (Oxford) spoke on the effects of fixatives on cells as seen under phase contrast. The juxtaglomerular complex of the rat kidney was shown by Drs. W. S. and PHYLLIS M. HARTROFT (Toronto); the granulation of this was clearly demonstrated, and it was stated that the number of recognizable complexes was doubled after a month on a low-sodium hypotensive diet.

Perinatal Pathology

The chair was taken first by Dr. T. J. CURPHEY (New York) and later by Dr. A. ANGRIST (New York).

Two speakers discussed the problem of sudden death in infancy. In the majority of 200 cases observed by Dr. JACOB WERNE (New York) acute respiratory disease was responsible for death. Widespread histological changes were seen, comparable with those present in known cases of fulminating infection and quite distinct from those in undoubted mechanical asphyxiation. Dr. D. A. SLADE (York) in a series of 30 cases found two main causes of death: acute respiratory infection, and asphyxia from aspiration, pressure of bed-clothes, etc. In the ensuing discussion a plea was entered for a co-ordinated investigation into the problem; some doubt was expressed regarding "regurgitation asphyxia" as a cause of death.

Dr. G. R. OSBORN (Derby) presented a study of vernix membrane in the lungs of infants, an important cause of death in the newborn secondary to intrauterine asphyxia. Subsequent speakers drew attention to the association with prematurity, whilst Dr. A. C. LENDRUM (Dundee) questioned whether the membrane consisted of vernix, and instanced the similar appearances seen in the lung in hypertensive and acute rheumatic states.

Dr. A. MACDONALD (Liverpool) reviewed the laboratory investigations of toxoplasmosis. Parasites were more frequently recovered by mouse than by egg inoculation. Serological tests should include both complement fixation and the Sabin dye method. Congenital toxoplasmosis was thought to follow primary infection of the mother during pregnancy, with transplacental passage during a phase of parasitaemia.

Dr. J. EDGAR MORISON (Belfast) observed that pneumonia in the stillborn and many cases of pneumonia in the first days of life resulted from intrauterine infection. Routine examination of the afterbirth showed a high incidence of chorionitis, indicating a possible mode of infection. The importance of dissemination of infection via the blood stream in neonates, and the frequency of non-specific oesophageal ulceration in cases with sepsis, were also emphasized.

Dr. J. W. GERRARD (Birmingham) discussed investigations into the pathogenesis of kernicterus. It was probably due to a metabolic disturbance, but hypoglycaemia *per se* did not appear to be responsible. Attention was drawn to kernicterus seen in premature infants in the absence of Rh iso-immunization.

Dr. H. S. BAAR (Birmingham) described the rare condition of congenital alveolar dysplasia, seen twice in 300 necropsies. Expanded bronchioles and alveolar ducts were separated by solid areas of undifferentiated mesenchyme. The condition was a true malformation and not a simple arrest of development.

Dr. KATERINA RHODES (Jamaica), in a study of liver disease affecting Jamaican children, confirmed the association with low protein intake. The earliest lesion observed was an exudation of unidentified material into the perivascular spaces of the liver, with subsequent organization. Parenchymal cells underwent atrophy, and eventually a severe diffuse fibrosis developed with disorganization of lobular architecture.

Pathology of the Pulmonary Circulation

The chair was taken in turn by Dr. J. F. MURRAY (Johannesburg), Dr. H. T. KARSNER (Washington), and Dr. R. KOURILSKY (France).

The session was opened by Dr. KARSNER, who gave a broad survey of the whole field of pulmonary vascular pathology. He drew attention to recent work on different aspects

of the field, and indicated the problems still needing explanation, in particular the lack of understanding of the physiological aspects.

Dr. A. A. LIEBOW (Newhaven) demonstrated his injection studies of the pulmonary vascular system by a series of beautifully coloured lantern plates. In chronic pulmonary disease, not only did the broncho-pulmonary arteries expand and divert aortic blood to the lungs, but the broncho-pulmonary veins also enlarged and drained bronchial and pulmonary venous blood back to the right heart. Enlarged plexuses of veins could be seen along the bronchi anastomosing with the pulmonary veins and forming a collateral circulation which might be of functional importance. The volume of blood carried by these collateral channels, both arterial and venous, was still unknown.

Dr. W. St. C. SYMMERS (Birmingham) described two cases of severe pulmonary hypertension in which the pulmonary arterioles showed fibrinoid necrosis and acute arteritis. He compared these lesions with those of polyarteritis nodosa and malignant hypertension, and concluded that they were secondary to the hypertension.

Professor J. MCMICHAEL (London) discussed the physiological aspects of pulmonary hypertension in mitral stenosis and chronic bronchitis and emphysema as studied by cardiac catheterization. In both conditions the resting pulmonary blood pressure might be normal, but it rose on slight exertion or in the presence of cardiac failure. It also rose with each attack of bronchitis and fell afterwards. There was no correlation between the pulmonary blood pressure and the degree of emphysema as measured by the residual air. There was some correlation between the pulmonary blood pressure and the degree of anoxaemia.

Professor J. GOUGH (Cardiff) discussed the frequency of fatal cor pulmonale in South Wales coal-miners. This occurred to a lesser degree in cases with focal emphysema, but was more frequent and severe in cases with "massive fibrosis," which he regarded as due to a combination of coal dust and tuberculosis. In these cases pulmonary hypertension could occur in the absence of any associated emphysema. There was extensive obliteration of pulmonary arteries in the fibrosed areas and little increase of bronchial arteries. In coal-miners' emphysema, unlike ordinary emphysema, the cardiac output was decreased.

Dr. C. V. HARRISON (London) showed that in a series of necropsies on cases of cor pulmonale due to chronic bronchitis and emphysema the degree of emphysema was variable and sometimes insignificant, whilst the bronchiolitis was more constant. He suggested that the bronchiolitis was probably the more important lesion.

Dr. R. KOURILSKY (France) demonstrated a series of cardio-pulmonary cases in which simultaneous tracings were taken by electrocardiography, phonocardiography, and cinedensography. By taking such tracings over different parts of the thorax it was possible to localize and to investigate the nature of limited lesions.

Dr. M. DE F. AMORIM (Brazil) described the lesions produced by injections of snake venom in rats, rabbits, and dogs. The lesions varied with the animal and the venom, but he drew particular attention to hyaline thrombi in small pulmonary vessels which he considered of diagnostic value in human cases of snake bite.

V. JOINT SESSION ON PIGMENT METABOLISM

A Joint Session of the Sections of Chemical Pathology and Haematology was held on July 19 to discuss pigment metabolism and haemoglobin. Professor M. POLONOVSKI (Paris) and later Professor C. RIMINGTON (London) took the chair.

The Porphyrias

Professor J. WALDENSTRÖM (Lund) opened with a discourse on porphyrins and the porphyrias. The latter were classified into congenital, acute, and porphyria cutanea tarda groups, and the clinical and biochemical features of each were distinguished. Study of the origin and inheritance of these inborn metabolic errors had become part of human genetics. Congenital porphyria was characterized by uroporphyrin-I production, which appeared to be a recessive character. On the other hand, the "acute porphyrias" were chronic disorders subject to severe acute episodes. There was frequent dominant inheritance, particularly in Northern Sweden, where a large number of families had been traced to a single pair in the seventeenth century. A colourless precursor, porphobilinogen, was excreted in the urine, and condensed to form varying amounts of uroporphyrins I and III. Recent evidence on the origin of haem-pigment precursors, particularly by the use of isotopically labelled glycine, suggested that substances of uroporphyrin type with eight carboxyl groups might be normal intermediates, but were rapidly decarboxylated.

Dr. R. E. H. NICHOLAS and Professor C. RIMINGTON (London) described the isolation and characterization of an unequivocal specimen of uroporphyrin III octa-methyl ester (m.p. 264° C.), the source being the red, copper-containing pigment of turacoa bird feathers. Uroporphyrins were of importance in the porphyrias, as well as in haem biosynthesis. Uroporphyrin-III esters were frequently obtained from acute porphyria urine, and these "Waldenström esters" did not contain hepta-carboxyl porphyrins in their experience, though variable amounts of series I isomer accompanied them. Discussion on these papers revealed wide awareness that the porphyrias might be less rare than was previously supposed, but that recognition depended upon thorough examination of both urine and faeces of suspected cases and of their relatives.

Professor C. H. GRAY (London) then described studies with isotopically labelled (N^{15}) glycine in congenital porphyria before and after splenectomy. Before operation the patient was excreting large quantities of uroporphyrin I. The activity of the excreted porphyrins indicated utilization of the glycine in their formation, and activity in the faecal stercobilin was such that much of it must have been derived directly and not through haemoglobin breakdown; it might represent a wastage during haem formation in the marrow erythroblasts. The rise of activity in the circulating erythrocyte haemoglobin was slower, but the subsequent rate of falling off indicated a reduced life span. Increased haemolysis was already recognized in some cases of porphyria. The effect of splenectomy was to reduce the uptake of labelled-glycine into the haemoglobin of erythrocytes, apparently through diminished haemopoiesis, and excess haemolysis ceased. Although uroporphyrin and urobilin excretion fell after splenectomy, the former effect was only temporary, and both substances continued to show the same high rate of incorporation of the isotope.

Haptoglobin Index

Professor M. POLONOVSKI (Paris) described his technique for determining the plasma haptoglobin, and assessed its value in diagnosis and prognosis of infective conditions. The peroxydatic function of pure haemoglobin caused rapid liberation of iodine from hydrogen iodide in the presence of hydrogen peroxide, but this soon fell off as the haemoglobin was oxidized by the iodine; the peroxidase enzymes liberated iodine smoothly under these conditions. If plasma contained haemoglobin, the latter united with the α_2-globulin in the plasma and the combination acted regularly, like a peroxidase. Professor Polonovski had devised an apparatus in which the iodine liberated under standard conditions could be titrated and the haptoglobin content of a series of plasma samples could be determined. The haptoglobin index rose in all infective states, and there was close correlation with the erythrocyte sedimentation rate. In tuberculosis the haptoglobin index might provide an earlier and more sensitive index of progress than the E.S.R. In haemolytic anaemias with haemoglobinaemia, fixation of the haptoglobin caused lowering of the index.

Heinz Body Abnormality

Drs. J. C. WHITE, J. V. DACIE, E. R. HOLIDAY, G. R. BEAVAN, and E. A. JOHNSON (London) described cytochemical and spectroscopic studies on the nature of the Heinz body abnormality of erythrocytes. The Heinz body in the red cell consisted of denatured globin united with a green haem, and fixed to the stroma or surface membrane by a layer of altered lipoid and stromal protein. Acetylphenylhydrazine readily formed Heinz bodies *in vivo* and *in vitro* under aerobic conditions. An experiment was described demonstrating spectroscopically that benzene was formed by the aeration of acetylphenylhydrazine in the presence of haemoglobin, the latter being irreversibly converted to Heinz-body pigment. Spectroscopic evidence was given that the green pigment still contained an intact haem, and a porphyrin liberated from Heinz bodies was described which closely resembled protoporphyrin and some of its derivatives.

VI. JOINT SESSION ON BONE METABOLISM

The final scientific meeting of the Congress was held on July 20 under the chairmanship of Professor DOROTHY RUSSELL (London). It was a joint meeting of the Sections of Histopathology and Chemical Pathology, at which metabolic aspects of disease of bones were discussed.

Histology of Bone Calcification

The opening paper was read by Professor S. L. BAKER (Manchester) on the histological aspect of the calcification of bone. Bone formation involved two distinct processes: the formation by osteoblastic cells of a protein matrix, and the calcification of this matrix. He discussed the composition of the matrix and suggested that even now its exact chemical structure was unknown. Under normal conditions the matrix was calcified very rapidly, but in certain pathological conditions, such as rickets and osteomalacia, the amount of non-calcified osteoid was greatly increased. He demonstrated the morphology of calcification, showing on the screen the intense haematoxyphil coloration of the earliest deposits of calcium. Under higher magnification he showed that the calcium was precipitated in small darkly staining spots surrounded by a lighter halo; later the haloes merged and the dots disappeared. The calcification of the bone matrix was dependent on the correct calcium/phosphorus balance of the tissue fluid and the proper development of the collagen and other components of the matrix. He demonstrated examples of lack of calcification due to aberrations of both these factors.

Effects of Vitamin A and Calcium on Bone Development

The next paper was by Dr. HONOR B. FELL (Cambridge), who described experiments on the effect of hypervitaminosis A on embryonic limb bones cultivated *in vitro* which had been performed in collaboration with Sir Edward Mellanby. The experiments were in two series—the first using non-ossified cartilage from six-day-old chick embryos, and the second with limb bones of well-developed mouse embryos. In the first series pairs of cartilages from the two limb-buds were explanted, one in a normal culture medium of plasma with embryo extract, and the other in the same medium containing an excess of vitamin A. She showed that the control explants grew to several times their original length and differentiated into remarkably normal-looking bone. The corresponding bones in the hypervitaminotic medium behaved similarly for the first two days. Then the growth became rapidly less and the proliferative zones disappeared so that the epiphyses became displaced from the rest of the bone. She showed that the chondroblasts remained healthy, but the matrix was greatly reduced in amount and almost lost its staining reactions. With the mouse embryos, paired bones were grown in similar media; in the control medium the bones grew normally for as long as 10 days, while in the hypervitaminotic medium the bone became smaller, the matrix lost its staining reaction, and frequently the bone fractured when being transplanted.

Dr. D. P. CUTHBERTSON (Aberdeen) discussed bone metabolism in relation to calcium intake and reproductive activity. He fed rats on a calcium-free basic diet to which various quantities of calcium were added in different groups of animals. He showed that a diet containing 0.36% of calcium was adequate, more was valueless, and that with even lower values calcification might appear practically normal. He also showed slides demonstrating the loss of calcium during lactation, and showed how much of it was made up during the subsequent pregnancy. Even on a very low calcium diet there was some repair in all cases during the period following lactation.

Bone Strength and Rickety Bowing

Professor G. H. BELL (Dundee) emphasized the importance of applying engineering principles in considering the strength of bones. He demonstrated his methods of measuring their breaking strength and elasticity, and the calculation of Young's modulus. He pointed out that the reduction of calcium intake led to the production of very thin bones, but, although the strength of the individual bones was much reduced, the breaking stress of the bony material remained unaltered. In rats on a rachitogenic diet the ash content of the bones was low and the breaking stress and Young's modulus were both reduced. He also pointed out that bowing of the bones occurred in rachitic pups but not in rachitic rats. In his opinion weakness of the bone by itself was not the cause of the deformities seen in rickets.

Metabolic Studies

Dr. D. M. DIXON (London) discussed the cause of the high citric acid content of bones. He pointed out that if calcium phosphate was precipitated from a medium containing citrates a certain quantity of the latter formed a co-precipitate. He showed slides demonstrating the increased amount of citrate that was precipitated with the calcium when magnesium salts were also present. He discussed the source of the citrate in the precipitating fluid and suggested that it might come from the metabolism of carbohydrate, bone having much less citratogenase than most other organs.

Dr. JANET VAUGHAN described work done in collaboration with Miss BARBARA KIDMAN, Miss BARBARA RAYNAR, and Miss MARGARET TUTT (Oxford, England) on the deposition of certain radioactive isotopes in bone, with special reference to strontium. She showed autoradiographs prepared from the bones of young animals after the injection of P^{32} and Sr^{89}. She suggested that these isotopes were taken up particularly by the growing cells of the bone, and the movement of the dense lines on the plates showed the way in which the growing cells altered their position as the bone grew. She also showed autoradiographs prepared from the bones of animals receiving Pm^{147} and Y^{91}. These isotopes were taken up in quite a different way from P^{32} and Sr^{89}. They showed a localized reaction beneath the epiphysial plate and to a lesser extent in the periosteum and endosteum throughout the shaft. In the compact bone there were numerous dots and lines which she thought indicated the position of blood vessels. All her work had been done on rabbits, and she emphasized the difficulty of cutting sections of non-decalcified rabbits' bones.

Bone Changes in Disease

Dr. IAN A. ANDERSON (Glasgow) described his metabolic studies in generalized diseases of bone. He indicated that diseases in which the amount of calcification of bone was reduced fell into three groups: osteoporosis, osteomalacia, and osteitis fibrosa generalisata. He emphasized the importance of oestrogens and androgens in stimulating osteoblastic function while the adrenal gluco-corticoids inhibited the

osteoblasts. He showed charts indicating the changes in the varying constituents of bone as a result of natural and artificial oestrogens and androgens.

The last paper was by Dr. H. A. SISSONS (London), who described the bone changes in five cases of Cushing's syndrome in which he had performed post-mortem examinations. He showed these changes with a series of beautiful lantern slides of microradiographs and histological preparations. In all cases the bone trabeculae showed little or no osteoblastic activity. Trabecular fractures were common, frequently causing vertebral collapse and spontaneous fractures of ribs. He thought that the callus formed was less in amount and that the osteoblastic activity and also vascularization of cartilage was less than in normal repair of bone.

CARE OF THE CHRONIC SICK AND AGED

INTERNATIONAL HOSPITAL CONFERENCE

The Seventh International Hospital Conference, which was held in Brussels from July 15 to 21, was presided over by Dr. René Sand, emeritus professor of social medicine, University of Brussels. More than 500 delegates from 23 different countries attended.

The central theme of this year's conference was the care of the chronic sick and the aged. In his opening remarks Dr. SAND referred to the growing awareness of the importance of this branch of social medicine. Two important papers followed. In the first, Dr. E. M. BLUESTONE, of the Montefiore Hospital, New York, chose as his subject "Integrating Acute and Chronic in a Combined Home–Hospital Pattern." He elaborated the principles underlying his own pioneer work in the field of home–hospital care for the chronic sick and the aged. Underlining his points by a happy choice of phrase, he said that a hospital bed was expensive, both to construct and maintain, but there was no substitute for it when it was genuinely needed. It followed that the criterion for admission to hospital had nothing to do with age and must be based only on the need for those facilities which a hospital alone provided. For all other patients he emphasized that individual care should be given wherever possible in their own homes. This aim could generally be attained with help subsidized from all available social and medical sources, but for those cases in which a home–hospital scheme of care proved impracticable a communal "substitute home" was the answer. But this was a substitute for the home and not for the hospital.

Dr. Bluestone reminded delegates once again that home care was one-quarter the cost of hospital care, and he showed that the setting-up of chronic hospitals was not only a bar to progress in the study of chronic disease but that it also needlessly duplicated expensive hospital plant. No one had ever suffered from nostalgia for a hospital bed, and, except through *force majeure*, a patient should remain in his family with extramural care radiating from the hospital into his home.

The Chronic Sick in Hospital

Professor PIERRE DELORE spoke on the care of the chronic sick and aged in hospital. The two guiding principles were to rationalize and to humanize. By the organization of home care the patient should be kept in his familiar environment. All too often a policy which took the line of least resistance classified patients as irremediable. Patients should be classified as acute, chronic, and elderly, and rehabilitation should be carried out as far as possible. For irremediable cases a modern type of home was needed, which must not be too large. In speaking of the special needs of the tuberculous, he deplored large institutions for chronic patients. The problem of the long-term psychiatric patient had to be squarely faced. For the aged sick geriatric departments should be organized in general hospitals. Finally, Professor Delore made a moving appeal for the restoration of a family code of ethics, whereby children would support their old parents and elderly people would find a place in the community.

The care of the chronic sick and aged was then discussed in four sectional groups. Under the chairmanship of Dr. T. Rowland Hill (England) the National and Regional Planning Group heard reports from Dr. H. O. PFISTER (Switzerland) and Professor R. E. TUNBRIDGE (England). Two main systems of care had to be considered—home care and hospital care—and the guiding principle was that whenever possible the chronic sick and the aged should be cared for at home. When this was not possible the solution might be: (1) residential homes for those not in need of actual medical treatment; (2) transfer to a general hospital for those in need of a complete medical examination for the purpose of diagnosis and treatment; and (3) admission to special beds for chronic patients, whether the mental, the tuberculous, or the elderly and chronic sick. Admission to such accommodation must always be preceded by adequate assessment in a general hospital.

The special needs of the various types of chronic patient were considered in detail, and emphasis was laid on the difficulty in most countries of recruiting nurses for such duties. In some countries this problem was met by setting up a service of assistant nurses with a shorter period of training. The question was raised whether the care of the chronic sick and the aged required mental and moral qualities of a higher order than did the care of other types of patient and whether the work was more suitably entrusted to middle-aged staff. Allocation of patients should never be regarded as final, since their changing needs call for an easy two-way traffic between hospital, home, and long-stay accommodation.

Units of Accommodation

The Planning, Construction, Equipment, and Maintenance Group, under the chairmanship of Dr. P. Van de Calseyde (Belgium), considered two papers, one by the Swedish architect Mr. G. BIRCH-LINDGREN, and the other by Dr. V. M. HOGE, of the U.S. Public Health Service. Both dealt with the planning of hospitals for the care of the chronic sick. It was not agreed that all cases of chronic diseases should be treated in special hospitals. If possible the units for chronic sick should be attached to general hospitals, either as an intimate part of their structure or, if physically separated, still sharing administration, food, laundry service, and facilities for acute treatment. It was felt desirable to group chronic patients according to the degree of their disability and not to mix those who are incurable with those capable of recovery. In planning units of accommodation full facilities should be provided for occupational therapy, re-education, and recreation. There was no agreement about the number of patients suitable for a nursing unit. The figure varied from 25 to 50 and was dependent on differing practices in each country.

Administration

Papers were read by Mr. MICHAEL REED, of the Ministry of Health (England), and Dr. BLONDEL (Belgium), manager of Verviers Hospital, to the group which considered organization, administration, and finance. Dr. E. B. Brooke (England) was in the chair. In the discussion that followed this group refused to identify the aged as synonymous with chronic sick, and the speakers insisted that care of the aged must be inspired by a sense of their dignity and by the value of family unity. The aged fell into three categories. These were the able-bodied, who could usually remain at home and hence presented no problem. Speakers of all countries emphasized the responsibility of the family. For those unable to remain at home the Dutch provided small houses grouped around a focal point.

The aged infirm were in need of continuous care but not of continuous medical care. These formed the kernel of the whole problem, because they tend to drift into hospital and there block acute beds. An arrangement was described whereby in some areas of Britain domiciliary visits were made by a consultant physician from the hospital, thus making possible a judicious use of beds in the acute hospitals. As long as the elderly patient was at home he remained in the care of his own family doctor, which was supported by all local services, whether statutory or voluntary, and by the full backing of the hospital. Account had to be taken of the "oscillating" cases. An old person of this type might require no help to-day, but to-morrow might be in urgent need of help, perhaps only of a temporary nature. At present real danger existed that the aged infirm might find themselves in an administrative "no-man's-land." Mental patients were in a special class: they should be fully assessed in an acute hospital before any decision was taken about their final settlement. The younger chronic sick, although numerically less important, presented individually a far more tragic problem.

In the third category were the aged suffering from acute diseases or other conditions requiring specialized medical care. Patients in this category presented no specific problem in the matter of accommodation, because they merely required temporary transfer to an acute hospital.

From the economic point of view the aged infirm should on no account be allowed to become a drain on the budget of the acute hospital, where it was four times more costly to maintain them than in special homes or in their own homes. It was bad to uproot them, so what was good economy was also good humanity. The problem of finance was not the same in Continental countries as in Great Britain, where the financial responsibility rests entirely with the State. This did not, of course, absolve the family from moral responsibility. All British speakers, in fact, insisted that this sense of family responsibility should be strongly encouraged. At the same time they emphasized that the need for voluntary co-operation remained as great as ever.

Personal Needs of the Patient

Dr. V. L. Parmar (India) presided over the important group which considered medical and nursing care, spiritual and cultural care, rehabilitation, and social service. Five papers were read, all dealing with the personal needs of the patient and the individual aspects of his care. Surveys of medical and nursing problems were given by Dr. MARJORY WARREN (England) and by Mlle. BIHET (Belgium). Dr. Warren stressed that in every case an attempt should be made to bring about maximum restoration of function and that the individual should be educated to live intelligently with his residual disability. Team-work was needed, and meticulous care for details. She concluded by describing the work of a geriatric unit, with special reference to the problems of elderly "chronic" patients, including incontinents, and to full rehabilitation and resettlement.

Mlle. Bihet felt that the well-known difficulty of recruiting nurses for this work would be lessened if they could nurse their patients under better conditions. She advocated smaller and better homes. The nurse should feel that she was a member of a team and not working in isolation. District nursing and home-help services must be developed. Miss G. P. MCCAUL (England) then outlined the principles of rehabilitation. Old people should be retrained in routine acts of everyday life. For the younger chronic sick occupational therapy should have a vocation as its aim.

Miss B. ROBERTSON (England) described the work of an almoner in a geriatric unit. She had to investigate the social conditions leading up to the patient's breakdown in health and also to relieve the anxiety of patients about their home cares while they were away in hospital. Plans for the patient's future care had to be set in train. Such plans, of course, were dependent on medical prognosis, and in this respect early contact with relatives was essential so as to prepare them for their future responsibilities. Old people's clubs formed a valuable focal point from which social contacts could be made.

TREATMENT OF ANTHRAX, BOTULISM, AND SNAKE-BITE

Some alterations have been made in the list of centres which keep emergency supplies of sera for the treatment of anthrax, botulism, and snake-bite, and the revised list of centres with telephone numbers is as follows:

The Dispensary, Newcastle General Hospital (Newcastle 35211); the Dispensary, Cumberland Infirmary, Carlisle (Carlisle 590); Seacroft Hospital, York Road, Leeds (Leeds 45194); Castle Hill Hospital, Cottingham, York (Cottingham 47372); Nottingham City Hospital, Hucknall Road, Nottingham (Nottingham 66292); Regional Blood Supply Depot, Brookland Avenue, Cambridge (Monday to Friday 8 a.m. to 10 p.m., and Saturday 8 a.m. to 6 p.m.; Cambridge 2536. All other times, Cambridge 87988); North Middlesex Hospital (Tottenham 3071); South London Blood Supply Depot, Stanley Road, Sutton, Surrey (Vigilant 0068); the Dispensary, Royal South Hants and Southampton Hospital (snake antiserum only) (Southampton 76211); Northampton General Hospital (Northampton 4680); Royal Berkshire Hospital, Reading (Reading 2231); Ham Green Hospital, Bristol (Bristol 31165); Swilly Isolation Hospital, Plymouth (Plymouth 4311); Pathological Department, Royal Devon and Exeter Hospital (Exeter 3519); Pathological Department, Royal Cornwall Infirmary, Truro (Truro 3029); Canton Infectious Diseases Hospital, Cardiff (Cardiff 960); the Dispensary, Selly Oak Hospital, Birmingham (Selly Oak 1361); the Dispensary, Manchester Royal Infirmary (Ardwick 3300); the Fazakerley Isolation Hospital, Liverpool (Aintree 2324).

A 24-hour service is maintained at each of the above centres. In addition, 10-ml. containers of anthrax antiserum for use prophylactically in persons exposed to infection may be obtained during the daytime from the following centres: Public Health Laboratory, 16–18, Edmund Street, Bradford (Bradford 24314); Public Health Laboratory, 184, High Street, Kingston-upon-Hull (Hull 35371); Bacteriological Department City Laboratories, 126, Mount Pleasant, Liverpool (Royal 3636); Central Public Health Laboratory, Colindale Avenue, London, N.W.9 (Colindale 6041 and 4081); Public Health Laboratory, General Hospital, Westgate Road, Newcastle, 4 (Newcastle 34920); Public Health Laboratory, General Hospital, Northampton (Northampton 347); Public Health Laboratory, County Hall, Taunton (Taunton 3451); Public Health Laboratory, Institute of Preventive Medicine, The Parade, Cardiff (Cardiff 8288).

The first international training course designed to help health officials in compiling uniform health and vital statistics has just been held in Geneva under the auspices of the World Health Organization. The 7-day course, grouping health statisticians from 14 countries, was designed as a guide in the use of the *W.H.O. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*. The manual (published in English, French, and Spanish) represents many years of efforts towards providing uniformity and comparability of health statistics, and sets out for the first time a single list for reporting both diseases and causes of deaths. Unlike international lists issued previously, it can be used by all health administrations and statistical offices as such and not merely as a basis for the preparation of national manuals. The manual also contains the various measures to be followed for the annual compilation of mortality and morbidity statistics by all W.H.O. member States.

Correspondence

Antihistaminics and Burns

SIR,—We were interested to read about the treatment of burns by oral antihistaminics carried out by Dr. A. E. Milne and others (July 14, p. 117), and also of the work of Drs. S. Shubsachs and D. A. Macpherson (July 28, p. 236). We would like to put on record our observations on the effect of the topical application of antihistaminic solutions in a series of approximately 60 cases of burns and scalds met with in the casualty department of St. Stephen's Hospital over the past seven months.

Acting on the same assumption as Dr. Milne and his associates, one of us (W. K. S.) considered that the local application of antihistaminic solutions would be more effective than the oral administration and would in this way prevent the side-effects of these drugs—i.e., drowsiness, giddiness, etc. Our experience has been for the most part limited to compresses of 2% solution of "benadryl" in sterile water kindly prepared by the chief pharmacist, Mr. Giles. The results observed are very promising and we think warrant a more detailed and controlled study. As in Dr. Milne's cases, the pain was relieved much earlier than in the controls, the erythema rapidly diminished in intensity, and blistering appeared much less frequently. Similarly, we found that the time factor was of importance, and the best results were obtained in those cases treated within the first four hours.

We were impressed by the lack of secondary infection, and this has led us to an investigation of the antibacterial properties of the drugs. An illustration of the gutter-plate method, using two strengths of benadryl, shows the relative inhibitory effects on the common pathogens which cause secondary sepsis. The nature of this effect is under study at present and will be the subject of a further communication.—We are, etc.,

W. K. SLACK.
EDDA BOESEN.
O. A. N. HUSAIN.

London, S.W.10.

FIG. 1.

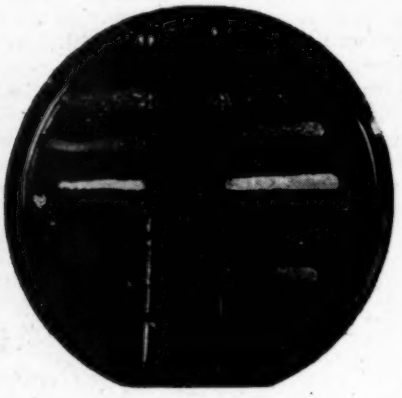


FIG. 2.

Plates with 2% benadryl (Fig. 1) and 0.2% benadryl (Fig. 2). Cultures (from above down) of *Pseudomonas pyocyanea, Staphylococcus aureus*, β-haemolytic streptococcus, *Corynebacterium diphtheriae, Streptococcus viridans*.

SIR,—I have read the letter in your issue of July 14 (p. 117) from Dr. A. E. Milne and his colleagues reporting the successful results obtained from the use of antihistaminics in the treatment of burns. Experiments in this field have led me to the same conclusions, and to the clinical use of antihistaminics, atropine, and "diparcol" (diethylaminoethyl-N-thiodiphenylamine) for burns. An account of this work appeared in *La Presse Médicale*, 1950, **58**, 922.—I am, etc.,

H. LABORIT.

Paris, 5e.

Heparin and Burns

SIR,—The letter of Drs. A. E. Milne, K. C. Balfour, and Joyce P. Yeoman (July 14, p. 117) adds interest to the action of heparin in neutralizing the toxic products of burns and of traumatic and inflammatory lesions. The use of heparin in the treatment of these conditions was developed from the findings of Pollard and Stoker (*Quart. J. exp. Physiol.*, 1946, **33**, 267) that they could not demonstrate heparin in the normal circulating blood in the absence of skin trauma, that they could find it in the blood, in measurable quantities, within a few minutes after a skin prick, and that it combined with a chemically basic factor which was formed in the region of the trauma.

Assuming that heparin, in physiological dilution, would neutralize these toxic products of trauma, it has been applied as a wet compress in a saline solution (0.44 unit/ml.) to heat burns, contused wounds, and various inflammatory lesions. The dressings are covered with a waterproof covering to prevent drying. During the past five years, in this two-man practice, this has been the routine treatment of the above conditions and in others, such as urticaria, chilblains, etc., in which an antihistamine-like action might be expected. The relief of pain, irritation, swelling, and the cleanliness of wounds so treated have been marked features. The antitoxic action of heparin in the treatment of acute oedema of the lungs in a case of burns has already been reported (*British Medical Journal*, 1947, **2**, 838). Heparin, 2,000–4,000 units intramuscularly or intravenously, has been rapidly effective in relieving six other cases of acute lung oedema in this practice. Its application, within 1–2 minutes of a skin burn, has been tested in industrial establishments: the relief of pain has been almost immediate and the formation of blisters prevented.

Heparin in physiological dilutions has no apparent antibacterial action, but, acting with a cofactor formed in connexion with traumatic and inflammatory lesions, it will inhibit the growth of certain bacteria *in vitro* (*J. Physiol.*, 1949, **110**, 26P). In much stronger solutions, and in protein-free media, it will do this without the presence of any cofactor (*J. Bact.*, 1950, **60**, 171).

Local heparin therapy has been tested under hospital conditions at the Leeds General Infirmary and the Ministry of Pensions Hospital, Leeds, by Mr. George Armitage (consulting surgeon) in the treatment of chronic ulcers. This surgeon also made a controlled experiment in a case which had both hands equally burned. One hand was treated with local penicillin and the other with local heparin. In the heparin-treated hand there was less pain, less swelling, and less slough than in the penicillin control. Mr. Armitage writes his opinion as follows: "In all the patients treated the continued cleanliness of the wound and the lack of surrounding oedema were marked features, and in my opinion confirm Mr. Stoker's conclusions that heparin acts locally as an antibacterial and decongestive agent."

In hundreds of cases treated with local heparin the only disagreeable effects have been (*a*) three cases in which purpuric spots occurred beneath the heparin compresses, and only where these were covering the damaged tissue, and (*b*) in a number of cases a feeling of tension in the skin adjacent to the burnt area or wound after three or four days' treatment. This was always relieved by reducing the strength of the heparin to half. This reduction of the heparin strength after three days is now made as a routine.—I am, etc.,

S. B. STOKER.

Ossett, Yorks.

Infertility

SIR,—In a brief but admirable summary of a subject on which many large books have been written Professor T. N. A. Jeffcoate (July 21, p. 167) could not but tread on some controversial grounds: (1) A period of two to three days' continence is too short for accuracy in semen analysis, the optimum time being four to five days. (2) The investiga-

tion of cases of azoospermia or oligozoospermia can be helped further by biopsy only in selected cases. Where the testes are small, soft, or atrophied, and where there is gross varicocoele or a history of mumps orchitis, biopsy is unnecessary. (3) The assessment of ovulation time by temperature charts is very approximate. In most cases the fertile date is 48 hours before the so-called ovulation drop in temperature. (4) Post-coital tests are, it is agreed, of limited value, but should not be entirely discarded, as they prove that spermatozoa do enter the cervical canal. (5) Variable counts can, and often do, respond to treatment, but gonadotrophic hormone therapy should be limited to bursts of six weeks; large doses are followed by a refractory period with a depressed count. Thyroxine, I think, gives better results than thyroid extract. (6) And lastly in my experience artificial insemination of subnormal semen offers a much better chance of conception than does coitus. It is one of the few really successful things we can do for the majority of subfertile males with fixed counts.—I am, etc.,

London, W.C.1. REYNOLD H. BOYD.

Anatomical Clinics

SIR,—The *British Medical Journal* of June 30 contains an interesting report of the recent London conference-course on Methods in Medical Teaching. Under the heading "Clinico-physiological Discussions" one reads (p. 1507): ". . . It was suggested that the same technique could be applied occasionally with reference to anatomy as well as physiology." Anyone interested may find in the *Canadian Medical Association Journal* (1946, **54**, 33) an account of more than a dozen years' experience of anatomical clinics. That experience now extends over twenty years.—I am, etc.,

University of Manitoba, Winnipeg, Canada. I. MACLAREN THOMPSON.

Fatal Barium Meal

SIR,—The medico-legal correspondent of the *British Medical Journal* reports in the number of July 14 (p. 124) an unexplained case of barium carbonate poisoning. His report mentions that the patient was given barium "sulphate" mixed with orange juice.

I recall giving evidence as an expert before a court in 1924 in a case involving death by exactly similar causes. In the case in question the barium sulphate was administered mixed with raspberry juice. It seems to me important that investigations should be undertaken to decide whether barium sulphate may be transformed into barium carbonate through the action of fruit acids (possibly in conjunction with high stomach acidity). It also seems highly probable that—if it should be by chance administered in error—barium carbonate may pass through the patient's stomach without dissolving if it is administered in a neutral mixture such as porridge, or something similar. In the case I refer to the result of the post-mortem showed the presence of barium carbonate in the stomach, while investigations at the local chemist's and in the hospital showed that the possibility of this having been administered by error could be excluded.—I am, etc.,

The Hague. W. WEISBACH.

Hernia after E.C.T.

SIR,—Now that electric convulsion therapy (E.C.T.) is being increasingly given in out-patient departments of hospitals and also in the course of domiciliary practice, may I draw the attention of your readers to one of the complications which may occur after repeated E.C.T.? Either inguinal or femoral hernia (which is a contraindication to E.C.T. unless curare is given first) may result directly from the E.C.T. in middle-aged and elderly persons. Unless this is borne in mind, and unless a physical examination is made before giving each treatment, several weeks or months may elapse before the patient's attention is drawn to the hernia on account of its size. Psychiatrists are not justified in assuming that patients referred to them are necessarily free from organic diseases. Recently, for instance, a London hospital referred a man aged 64 for the treatment of his "depression." He had been an in-patient there for investigation of his heart, and the physician's report stated that, apart from a systolic murmur at the apex, nothing abnormal was detected in any of the organs or systems. When examined here he had bilateral large inguinal herniae (which he has had for over twenty years), which were difficult to reduce, and a cardiologist who at my request did an electrocardiographic investigation found bundle branch block.—I am, etc.,

Sutton, Surrey. M. N. PAI.

Ethics of Prefrontal Leucotomy

SIR,—I have read with interest Mr. J. Schorstein's letter (July 28, p. 239). Although one can only endorse the emphasis he places on the moral as well as the psychiatric evaluation of leucotomy results, I am unable to follow his argument on the problems in the case he cites (Dr. G. D. F. Steele's article of July 14, p. 84).

One may surely have doubts about the excellence of a leucotomized patient as a judge of moral values or as a mother of children; one may realize that "functional" efficiency, even if obtained, lacks qualities one would wish in a perfected individual; one may recognize that in losing the ability to suffer (if this really occurs) one is also losing the possibility of experiences proper to "man in the human situation"; one may recognize, and deeply regret, all this—and yet not feel shocked at what has been done if, on these counts, the post-operative condition of the patient presents advantages not present pre-operatively. One is not dealing with individuals who, possessed of full mental, spiritual, and physical efficiency, are being subjected to procedures that lessen this efficiency, but with individuals of decreased or even absent efficiency for whom, in the majority of cases, no other hope of improvement is entertained.

Does the appearance of a post-operative inability to provide one's husband with comforts beyond that which depend on "the cooking of meals and sweeping of floors" offset the disappearance of a pre-operative inability to leave one's bed, and subjection to panic storms and suicidal drives, even supposing that a post-operative inability such as Mr. Schorstein describes does in fact exist? However little comfort a leucotomized wife may be in the trials of life, experience suggests that her husband is usually emphatic in his preference for the post-operative result.

If the loss of ability to suffer is to be taken as a criterion of the moral value of the operation, one wonders if there is any essential difference between the removal of a peripheral source of suffering—a breast carcinoma, for instance—and the removal of the more centrally placed fronto-thalamic radiations. In their relation to suffering are not the peripheral tissues and the central nervous system but different parts of the pathway that leads from the exterior to the personality itself? One may surely acknowledge the possible moral value of suffering and yet feel justified in taking action when the suffering is so excessive that not only is all useful activity, spiritual as well as physical, suspended, but life threatened by suicide. Spiritual euthanasia, if such is not a contradiction in terms, consists rather in allowing such a suspension of useful activity to continue than in attempting to overcome the paralysis and allow the individual, deficient as he may be in some respects, to go forward to whatever goals are still open to him.

As with any surgical mutilation, one wishes it were not so. One hopes that in future enlightened ages psychiatry will do away with the need for leucotomy. In the meantime, to foster the greater evil for fear of the lesser would be folly.—I am, etc.,

Brentwood, Essex. D. ANTON-STEPHENS.

SIR,—Mr. J. Schorstein's letter (July 28, p. 239) criticizing the choice of leucotomy in a case described by Dr. G. D. F. Steele (July 14, p. 84) is, I feel, unjustifiably harsh. It seems to me important that the patient attempted suicide after a

period of treatment and observation in hospital, and that a trial of conservative measures was made over a reasonable period of eighteen months. During that time the case proceeded without substantial remissions from bad to worse. I have a conviction on re-reading the evidence that this operation has probably prevented one more suicide. This also is a moral consideration.—I am, etc.,

Bristol. GEORGE LIONEL ALEXANDER.

Mesencephalitis and Rhombencephalitis

SIR,—The article by Dr. E. R. Bickerstaff and Professor P. C. P. Cloake (July 14, p. 77) recalled to my mind six similar cases which I saw in India in 1942. Although occurring sporadically over nine months, they made a very distinctive group.

The most striking common features were the drowsiness combined with ptosis and facial paralysis or paresis, which with a suffused face gave a very characteristic appearance. The patients could be roused and would answer rationally, but fell asleep again immediately, even during examination. As the drowsiness passed off four out of the six had for a while reversed sleep rhythm. Other features such as ataxia, dysarthria, nystagmus, loss of reflexes, and sensory loss were present to a varying extent in the different cases. The onset was gradual and was preceded by general malaise, headache, and pyrexia for about a week. The course of the disease was very like that of the Birmingham cases, though in none of mine was the brain so widely affected. Four out of the six began to recover rapidly after three or four weeks; after about eight weeks recovery was apparently complete. One patient developed a typical Parkinsonian facies, tremor, and gait which were still present when he was invalided home six months after the onset of his illness. The sixth patient—the first one of the series—became wildly delirious soon after admission and died. The pathologist reported "acute congestion of the basal ganglia with necrotic changes in the ganglion cells and chromatolysis of the nuclei."

The cerebrospinal fluid varied, being normal in two cases, showing increased protein in three and a lymphocytic pleocytosis in two of these (all three patients with abnormal fluid had neck rigidity in the early stage of their illness). Blood counts were normal, and no malarial infection was found, nor did treatment for malaria influence the course of any of the cases. Various other investigations, though necessarily limited, were negative.

These cases all occurred in British personnel in one area, in which the population remained relatively stable. During the same period 29 cases of poliomyelitis were seen, 23 of them occurring in one month, and the remainder sporadically over the rest of the nine months. Seven of the 23 epidemic cases were severe, with a rapidly spreading lesion including the bulb, and these all died. The difference between these seven cases and the six just described was striking, not only in their clinical features but in the course which they followed, so much so that I was reluctant to classify the latter group as polio-encephalitis and wondered at the time if they could be encephalitis lethargica.—I am, etc.,

Neston, Wirral. K. COBBAN.

SIR,—Dr. E. R. Bickerstaff and Professor P. C. P. Cloake describe three cases (July 14, p. 77) of bulbar palsy which recovered completely; structural damage of the central nervous system was therefore negligible even at the time of the moribund condition. They say, "The gradual development to maximal disability with subsequent recovery seems to eliminate vascular thromboses, haemorrhages, or emboli." However, the clinico-pathological picture is quite well understandable as a local cerebral tissue acidity inadequately corrected by the blood flow.

The functional paralyses are attributable to an increase in the tissue acidity, because it is known that a slight increase raises the threshold of stimulation enormously.[1] It is also known that a local tissue acidity causes hyperaemia, venous congestion, and, if severe, thromboses. Such vascular changes may be presumed to have existed in the authors' cases, since they are found in all encephalopathies (toxic, virus, traumatic, or after anaesthetics).

Cerebral anoxia occurs with vascular thrombi, emboli, or vascular spasm. Whether local or general, the anoxia changes cerebral sugar metabolism to lactic acid production. Vitamin B_1 deficiency arrests the metabolism at the stage of pyruvic acid. Viruses are nucleoproteins (like genes), and change cell metabolism to duplication of the nucleoprotein. All the clinical effects of a virus infection may be ascribed to the reactive vascular pathology.

Where the vascular flow corrects the acidity there will of course be no neurological signs with a virus infection. Where it is inadequate, or where there is summation with another source, then a vascular lesion will result. The *site* of the paralyses, for example in poliomyelitis, is thus determined by "tonsillectomy, muscular fatigue, inoculation, and local infection."[2] An inflamed area determines the site of the localization of particles or bacteria from the blood stream.[3] Lethargic encephalitis (and occasionally influenza virus) infections cause midbrain diseases when associated with nasal sinus sepsis.

An analogous abeyance of the central nervous system function with complete recovery is also found in cases of mental disease[4]; and in those cases which come to necropsy I have often found thrombi in the carotid or main cerebral arteries[5] as the related associated pathology. The importance of the peripheral contributory lesions—e.g., chronic septic foci—in treatment is thus manifest, and this is confirmed by the higher recovery rate in those hospitals where such treatment is done.

—I am, etc.,

Birmingham. F. A. PICKWORTH.

REFERENCES

1 Koenig, H., and Groat, R. A., *J. Neurophysiol.*, 1945, **8**, 267.
2 McAlpine, D., *British Medical Journal*, 1951, **1**, 1511.
3 Menkin, V., *Dynamics of Inflammation*, 1940, 126, New York.
4 Pickworth, F. A., *British Medical Journal*, 1938, **1**, 265.
5 *New Outlook on Mental Diseases* (in the press).

Bacillary Dysentery in Britain

SIR,—Your leading article (July 14, p. 102) asserts that official notification of dysentery means in most cases notification of the isolation of a shigella and that many of the notified are symptomless excreters. In my own experience this is untrue, and certainly a careful reading of the preceding sentences of your article yields no clear evidence to support it. A rough concordance of the figures of statutory notifications and of persons from whom shigella-positive stools have been examined by the public health laboratory service is no proof that the persons numbered in the two lists are the same. Only a study of those persons, by name, could establish this and lead to the conclusions stated in your article.

Medical officers of health have long been aware that Sonne dysentery is under-notified and it still is, though it is difficult, save in institutions such as nurseries and schools directly under their supervision, for them to gauge in any way the degree of under-notification in the community. There are times when it seems as prevalent in the community as it is found to be in an institution under close supervision.

Notification is legally reserved to *cases*, not healthy carriers, though no one doubts that a number of the latter are notified, and medical officers of health would, I believe, generally desire that they should be notifiable, formally, as carriers. A number of persons with shigella-positive stools but apparently at the time unaffected show signs of the disease a few days later, and then become notifiable as cases. It is also true that not infrequently in a family several members will show at short intervals symptoms of dysentery in different degrees ranging from transient and trivial diarrhoea to the classical complex; perhaps one or two may have been found bacteriologically positive for Sonne dysentery, and the others are also then quite properly notified without necessarily being bacteriologically proved themselves.

Another thing not mentioned is the fact that medical officers of health have contributed substantially to the better notification of the disease by following up in epidemiological inquiry (as indeed is their statutory duty) cases of dysentery whether notified formally or brought to their notice informally. In this work the public health laboratory service has rendered invaluable and most willing and essential assistance, to which I would pay sincere tribute.

The notification of dysentery is especially important when the disease occurs in a food or milk handler, and to await confirmation by a bacteriological examination before

notifying the medical officer of health, informally if desired, is to risk infection of a large number of people. Again, acute diarrhoea in a household of which such workers are members, even if not themselves at that time suffering from the disease, is also a matter of concern to the medical officer of health, and notification again becomes important. There is a great deal to be said for notification of infectious disease to be based on reasonable suspicion on clinical grounds rather than on bacteriological proof, though dysentery is, as you say, often clinically insignificant to the patient, but it may be more serious to another infected by that person.

In food poisoning, *suspicion* of the disease necessitates notification, and, in regard to food workers at least, the same should apply to dysentery; in fact, a close and friendly relationship between the general practitioner and the medical officer of health in these matters is imperative if dysentery is to be controlled—another important point not mentioned in your article.

Long-continued exclusion from school of older children who are dysentery carriers is a procedure of doubtful value and is harmful to the welfare of the child. Your suggestion that bacteriological examinations of new entrants to nurseries and schools may be necessary is quite unrealistic. The really important thing is close attention to personal hygiene throughout the population.—I am, etc.,

E. D. IRVINE,
Medical Officer of Health.

Exeter.

"War" and "Peace"

SIR,—The members of this committee, in common with others on the *Medical Register*, have received the questionary circulated by the Central Medical War Committee. We recognize that any responsible Government must take steps to protect the public and to organize medical resources against an emergency. On the eve of almost certain war, such a document would not be unreasonable. We feel, however, that its appearance and tone at the present time and in the present international situation themselves contribute to the risk of war and reduce the possibility of conciliation. In our opinion, the present circumstances do not parallel those which led to the preparation of a similar questionary in 1939. That document was issued in the face of imminent war. By taking a comparable step at the present time we run the risk of creating an unwarranted impression of emergency at home and increasing suspicion abroad.

The urgent necessity of to-day is, in our view, conciliation and reduction of international tension. The measures which are being undertaken to put our community on a war footing in time of nominal peace are tending to defeat those ends. We take the strongest possible exception to the unseasonable extension of this process to the medical profession.—We are, etc.,

DUNCAN LEYS,
Chairman.
L. S. PENROSE,
Secretary.

The Medical Association for the Prevention of War,
London, W.11.

Dental Anaesthetics

SIR,—Mr. D. J. Ritchie (July 28, p. 239) should not be ashamed of his dental qualifications. May I, another dental surgeon, reply to his extreme views on general dental anaesthetics? I have used only local analgesia, as Mr. Ritchie advocates, for a period of five years during my Army service. Having returned to my own practice I can say without hesitation that general dental anaesthesia has its place, and without it a service of great value to the frightened or distressed patient would be lost.

I would agree, Sir, that in cases of anaesthetic resistance the addition of some stronger agent than nitrous oxide and/or premedication is essential. The risk of foreign bodies being inhaled in the chair must be weighed against the risk of trauma or infection which might be caused by intubation and packing off the pharynx, with the patient's additional mental anxiety due to being transferred to an operating theatre and a stay of some time away from home in a hospital bed.

It would seem, Sir, that what is needed is not so much the condemnation of nitrous-oxide anaesthesia as a greater skill and knowledge of its limitations to enable the greatest possible use to be made of its undoubted advantages.—I am, etc.,

C. N. JEFFRIES.

Birmingham.

Penalties for Sexual Offences

SIR,—Recently it was reported by the press that a rear-admiral lost his pension of £1,000 per annum and was sent to prison for 18 months for improper offences against five boys between the ages of 13 and 15. While such offences cannot be condoned, the penalty for them has always seemed to me to be out of all proportion to the crime and fails to make any allowance for the fact that such crimes are due to a disorder of the body and mind, whereas far worse crimes frequently escape punishment when due to disorder of the mind alone. Therefore it seems to me that the time is overdue for the medical profession to give a lead in urging more humane consideration in cases of this kind. It is noteworthy that similar behaviour between females is not, apparently, a criminal offence.—I am, etc.,

G. W. FLEMING.

Gosport, Hants.

POINTS FROM LETTERS

Procaine for Hypertension

Dr. GEORG BIRO (Vienna) writes: I use intravenous procaine treatment in cases of essential hypertension with excellent results. After treatment the increased blood pressure returned to normal, remaining there without any further treatment.

Scheme of Treatment.—1st to 3rd day: ½% procaine solution, 1 ml.; 4th to 6th day: 1% procaine solution, 1 ml.; 7th to 10th day: 2% procaine solution, 1 ml.; 11th to 20th day: 2% procaine solution, 2 ml.; 21st to 30th day: 2% procaine solution, 4 ml.; 31st to 40th day: 3% procaine solution, 4 ml. All injections are to be given very slowly (1 ml./min.), intravenously, with patient reclining. I have never seen any side-effects following this treatment.

Anaesthetics in Casualty

Mr. E. K. GARDNER and Dr. J. W. MONRO (Leytonstone, E.11) write: Dr. J. G. Bourne's letter and your annotation (June 9, pp. 1314 and 1330) come as timely reminders. . . . Among the difficult cases we are called upon to anaesthetize in casualty we would include the elderly hypertensive patient with a fracture and the fit young man for manipulation of a large joint. In the former "anoxic anaesthesia" is dangerous and in the latter useless. . . . Cyclopropane with no premedication may aggravate any cardiac arrhythmia present, and indeed initiate cardiac irregularities; nevertheless we have found cyclopropane of great value in the elderly patient, as there need be no anoxia and there is rapid recovery of full consciousness. Local analgesia has a definite place in the treatment of recent fractures, especially those in the neighbourhood of the wrist and ankle joints. For manipulations in fit young patients, thiopentone or cyclopropane has been our method of choice up to the present time: in future we intend to include in our technique a muscle relaxant as required. Occasionally gas-oxygen (about 90:10) under pressure has been used, but the degree of relaxation was rarely adequate. . . . For children under 6 years we prefer to use open ether with or without ethyl chloride. Muscle relaxation is not essential in dental cases, and we are entirely satisfied with nasal gas-oxygen under pressure, save for a total extraction in unfit subjects. We agree that there should be more teaching in this specialized sphere of anaesthetics. We have been puzzled to understand why so-called "minor ops." are apparently so often regarded as casual by all but the patient. We think, in particular, that the question of premedication should receive more attention.

Correction.—In the obituary notice of Sir Walter Johnson, which was published in the *Journal* of July 21 (p. 180), a reference was made to papers published by Johnson, Lloyd, and Ramson; the last name was wrongly spelt, the author being Dr. P. H. Rawson.

Obituary

J. H. DRYSDALE, M.D., F.R.C.P.

We are indebted to Dr. Geoffrey Bourne for the following appreciation: Some men achieve professional eminence by their original work, and some by professional and social activities or by purposeful ambition. Drysdale avoided all of these paths and even scorned them, but in spite of himself he became a great figure. He was the finest clinical teacher of his generation at St. Bartholomew's and exerted a profound influence which still lingers, although he retired from the hospital staff in 1924. He was wealthy, but his bachelor life was abstemious. He avoided private practice, preferring to concentrate his great gifts upon the hospital work which he loved. He had a great analytical mind and a fearless and unhampered power of criticism, and this made him at times somewhat unpopular among his colleagues and superiors. To his juniors, however, he was invariably kind, considerate, and helpful. The opinion of the most junior clinical clerk was respected by him if it could be logically substantiated. His yardstick was the scientific method and truth for truth's sake. He never assumed a position of superiority, and abhorred pomposity, verbosity, and loose thinking. In his teaching he attempted to explain symptoms and signs of disease in terms of disturbance of physiological, anatomical, and physical principles. Such was his skill at perceiving fundamentals and impressing his pupils with them that he evoked in them a sense of confidence, most valuable in the face of clinical difficulty. His method of teaching was by skilful question and answer, and by its use he could elicit from a first-time student, building the subject up from step to step, the probable changes in the heart and systemic and pulmonary circulations in, for instance, a case of mitral stenosis. He taught people how to think, how to apply the principle of controls, and how to see through speciousness and pretence. His priceless gifts to medical teaching can be remembered, but can never be truly assessed by those who know him only as a legend.

Dr. Harold F. Renton died suddenly at Doncaster on July 26, aged 66. Born at Harrogate in 1884, he graduated M.B., B.S. (London) at Guy's Hospital in 1910 and proceeded M.D. in 1912. After holding residential hospital appointments at Guildford, Leeds General Infirmary, and Bradford, he came to Doncaster in 1916. During these years he led an active athletic life and during his student days at Guy's was a representative for Great Britain at the Olympic Games. It was not long before he became a very widely known and greatly respected general practitioner. He took a leading part in the social side and committee work of general practice. At the time of his death he was chairman of the Doncaster Local Medical Committee, following many years' service on the original Doncaster Panel Committee. He was also a member of the Doncaster Executive Council, and had been chairman of the Doncaster Division of the B.M.A. and President of the Doncaster Medical Society. It may well be, however, not for this side of his work and activity—most useful though they were—that he will be best remembered. He was an immensely loved general practitioner. His outstanding personal appearance, almost legendary fastidiousness in dress, and devotion to the highest possible standards in courtesy and good manners were only the outward signs of his adherence to a very high standard of ethics and of his utter belief in the discipline of careful, devoted work. His sympathy, kindness, and tact were also enjoyed to the full by his colleagues of all ages. They knew he would always support them with a robust loyalty. Such loyalty will be for ever an example to his fellow practitioners. Men of his stamp are rare, and it is sad to think that this charming, courtly doctor will no longer grace the professional life of Doncaster. He leaves a widow and a married daughter, to whom we offer our deepest sympathy.—R. W. L. W.

John Probert Mostyn, registrar to the gastro-enterological unit at Whittington Hospital, died on July 26 at the age of 27. Mostyn's home was in Llandrindod Wells, Radnorshire, and he received his medical education at University College and University College Hospital, where he was awarded the Fellowes Gold Medal in 1946. He graduated M.B., B.S. in 1947, and later held the posts of house-physician at the Swansea General Hospital, house-surgeon at the Caernarvon and Anglesey Hospital, Bangor, assistant medical officer at Alder Hey Children's Hospital, Liverpool, and house-physician to Dr. Russell Fraser at Hammersmith Hospital. He gained his D.C.H. in 1949 and M.R.C.P. in January, 1950, and was elected to the appointment at the Whittington Hospital about sixteen months ago. For six or seven years Mostyn had known that he suffered from a condition which would prove fatal while he was still a young man. Nevertheless he threw his whole energy and enthusiasm into his work, and his short professional life was a model which inspired his contemporaries. His last few months at the hospital were a continual battle against failing health; even so, he carried on part-time work until a few weeks before his death. Those who knew him will remember in all humility his courage and demeanour at that time. Our deepest sympathy goes to his family in their tragic loss.—A. H. J.

Medico-Legal

DEATH ON THE TABLE

[From Our Medico-Legal Correspondent]

A married woman of 25 underwent an operation for appendicitis at the Meath Hospital, Dublin, on March 12. The surgeon examined her beforehand and found nothing amiss. She was given premedication with "omnopon" and scopolamine at 8.40 a.m., and at 9.15 a.m. anaesthesia was induced with pentothal sodium and continued with nitrous oxide and oxygen. She was from the first restless and would not relax, even though "flaxedil" was given, and the surgeon had to postpone the operation for about half an hour. She produced a large amount of mucus, and an intratracheal tube was passed. Ether was added slowly, first by closed and then by open circuit. The patient settled down, but relaxation remained poor and the surgeon was obliged to suspend the operation.

After about three-quarters of an hour the anaesthetist, in accordance with the usual practice of the hospital, handed over to the house-surgeon. The patient's condition was then satisfactory. The anaesthetist warned the house-surgeon, who had had plenty of experience of anaesthesia, that the patient was excreting a good deal of mucus and that he should not press the anaesthetic even though relaxation was not complete. After a time the house-surgeon noticed that respiration was becoming shallow and told the surgeon, who at the same time noticed that the patient had relaxed for the first time. The anaesthetic was stopped, the anaesthetist was recalled, and artificial respiration was begun, but neither this nor injections of nikethamide, procaine, and adrenaline revived the patient.

The pathologist who performed the necropsy told the coroner's jury[1] that in his opinion death had been due to

[1] *Irish Times*, March 20.

cardiac failure resulting from previous heart disease and pulmonary tuberculosis, aggravated by the anaesthesia. The heart disease was not dangerous in itself, but the lung lesions appeared to be recent.

The jury returned a verdict in accordance with the evidence, attaching no blame to the doctors or the hospital.

Medical Notes in Parliament

Hospital Registrars

Replying to Dr. Barnet Stross on August 2, Mr. MARQUAND said his discussions with representatives of the medical profession had reached an agreement that the normal period of training of a senior registrar should be increased from three years to four, and that, in consequence of this and other factors considered during the discussions, the total training establishment of senior registrars in England and Wales should be 960 instead of the 600 suggested on a three-year training basis at the end of last year. They had also agreed broadly on the distribution of this total by specialties. He proposed to enter into discussions with regional hospital boards and boards of governors about their shares of the totals in the light of the proposals which they had submitted to him. As regards registrars, whose appointments do not normally last more than two years, he proposed to give boards, in the course of his discussions with them, some further guidance about the place of this grade in the hospital service. He had decided for the time being, with the profession's agreement, to leave boards to fix their own establishments of registrars in the light of that guidance, subject, however, to review when the reports of the teams now examining the medical staffing of hospitals had been received and considered.

Royal Assent

In the House of Lords on August 1 the Royal Assent was signified to the Rural Water Supplies and Sewerage Act, the Dangerous Drugs Act, the Midwives Act, the Midwives (Scotland) Act, the Nurses (Scotland) Act, the Guardianship and Maintenance of Infants (No. 2) Act, the Rag Flock and Other Filling Materials Act, the Rivers (Prevention of Pollution) Act, and the Rivers (Prevention of Pollution) (Scotland) Act.

Leeds Regional Hospital Board Expenses

On July 27 Colonel M. STODDART-SCOTT asked the Minister of Health about the expenses incurred by the Leeds Regional Hospital Board for their accommodation at the Queen Hotel, Harrogate. Mr. H. MARQUAND told him that the rent paid was £4,000 per annum, and the lease was for 25 years; the hotel was used as the board's headquarters, and also would house a preliminary training school for nurses and later be a hostel for nurses from Harrogate hospitals. The resident staff were the steward and his wife, responsible for catering, domestic work, and stores; they were paid respectively £540 and £340, less £140 each for board.

Colonel STODDART-SCOTT further asked why members of the regional board and their families had been accommodated at the hotel, what charges had been made, and what accommodation in the hotel was used by administrative staff. The Minister replied that some members of the board had to come long distances for board and committee meetings on successive days, and at present four rooms had been placed at their disposal on such occasions. Their families had not been allowed to use these rooms except when once, in special circumstances, a member's wife was allowed to for one night only. The charge was 10s. a night for the room and 2s. 6d. for each meal. In answer to a question about the board's cars, Mr. Marquand stated that there was only one, which was used to transport the chairman and members when visiting hospitals. It was also used to meet members at the station when they came from distant parts of the region to attend meetings. He had no figures to show the cost per mile.

Chemicals in Food

Mr. F. WILLEY, for the Ministry of Food, said on July 30 that he had no reason to believe that lithium chloride was used in Britain as a substitute for salt in food products, or in bread-baking or confectionery manufacture. If he saw signs of its being introduced he would forbid it. Mr. Willey said this in reply to Dr. Barnet Stross, and also announced that neither dulcin nor P 4,000 was being put into food or drink in this country. Apart from sugar, glucose, and allied carbohydrates, the only sweetening agent at present in use was saccharin. Dulcin had been used, but he was glad to say that its use had been abandoned.

Leprosy in the Colonies

Mr. R. W. SORENSEN on August 1 asked what progress had been made in leprosy research and treatment in the Colonies.

Mr. JAMES GRIFFITHS replied that important research work was being conducted with promising results, particularly in the development of a form of sulphone treatment by oral administration requiring the minimum of medical supervision. Exact statistics of the disease were not readily available. Some indication of the problem was given by a comprehensive survey of the East and Central African territories last year, which resulted in an estimate of 265,000 cases in the region. Surveys were in progress in West Africa. The newer forms of treatment were everywhere available.

Admission of Emergency Cases

Mr. F. MCLEAVY on August 2 asked what action the Minister of Health proposed arising from the verdict of a Bradford coroner's jury in the case of Eileen Cunliffe.

Mr. H. MARQUAND said he had asked the regional hospital board to ensure that it was clearly understood at each of the hospitals concerned that in no circumstances might a patient who needed immediate admission to hospital be sent on to another hospital while still an "emergency," and that the casualty departments were always under the effective supervision of experienced medical officers. He added that, after a very full investigation of the case, the board had drawn the attention of the medical officer concerned at the children's hospital to the fact that she was seriously at fault in not seeing the child, and had informed the then senior surgical registrar at the Royal Infirmary that in its opinion he could not escape full responsibility for failure to admit her. The board decided that the casualty officer at the latter hospital should be completely exonerated from all blame.

Identity Cards and Treatment

Mr. G. WILLS on August 2 asked the Minister of Health whether dental and medical practitioners were entitled to demand the production of their patients' national identity cards.

Mr. H. MARQUAND said they were not so entitled. Patients desiring treatment under the National Health Service were asked to give their national registration numbers as an additional means of identification, and normally did so.

Proprietary Medicines

Dr. BARNET STROSS, on August 2, asked Mr. H. Marquand what action he would take to protect the public from some proprietary medicines which were not only expensive but useless, and whether he would initiate an examination of the manufacture of proprietary medicines. Mr. H. MARQUAND, in reply, said there was already a considerable degree of legislative control over proprietary medicines, and he had the

matter generally under constant consideration. He knew that there were special provisions in France, but he had not had time to study them.

Dr. CHARLES HILL asked Mr. Marquand to bear in mind that "proprietary" covered not only useless but immensely valuable products. It was desirable that there should be a clarification of terms. Mr. MARQUAND said it was certainly true that there were very valuable proprietary medicines. The Central Health Services Council had a special subcommittee of the Joint Council on Prescribing, under Sir Henry Cohen, which was surveying the whole field of prescribing. This included a survey of the whole field of pharmaceutical preparations available for prescribing. A number of proprietary medicines and preparations had already been listed by Sir Henry Cohen's committee. The names of those which were not desirable for prescribing had been notified to general practitioners. There was no interference with the right of practitioners to prescribe.

Increase in Number of Deaths

On August 2 Sir HERBERT WILLIAMS drew attention to the fact that the deaths in England and Wales in the three years following the introduction of the National Health Scheme were 1,576,000 as compared with 1,492,000 in the previous three years, an increase of 6%.

Mr. MARQUAND replied that the increase in the number of deaths was attributable to the increase in population between the two periods and the effect of the influenza epidemic early this year.

Bequests of Eyes

Mr. H. M. KING asked the Minister of Health on August 2 whether he would consider the Anatomy Acts of 1832 and 1871 in such a way as to make it easier for persons to bequeath their eyes for use after death to cure the sightless. The Minister replied that the matter was not governed by the Anatomy Acts but by Common Law.

Doctors in Scotland.—Medical practitioners under contract to executive councils in Scotland at January 1 numbered 2,402.

Accident Deaths.—The provisional number of deaths registered in England and Wales in 1950 as due to accidents, including drowning, other than road vehicle accidents is 9,582.

Age of Consent.—The Lord Chancellor proposes to ask the Royal Commission on Marriage and Divorce to consider whether any amendment should be made in the law relating to women who go through a marriage ceremony when under 16 years of age and have children.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on July 14 the following medical degrees were conferred:

D.M.—D. A. McDonald, J. D. Green.

B.M.—D. G. Cottom, G. B. Batchelor, P. H. Cave, M. C. Gill-Carey, C. N. Smyth, H. E. Webb, A. W. Beard, R. G. Richardson, P. V. Skinner, H. E. Brown, E. J. Elkington, A. S. Gardiner, F. R. Wells, G. R. Webster, Mrs. Patricia M. Strang, Toba E. Zaiman, *J. H. Mott, *R. M. Acheson, *R. G. Willison.

The following elections are announced: *Radcliffe Scholarship in Pharmacology*, R. H. O. Parker. *Horatio Symonds Studentship in Surgery*, Dr. A. M. N. Gardner. *Theodore Williams Scholarship in Anatomy*, M. W. B. Bradbury. *Theodore Williams Scholarship in Physiology*, T. D. R. Hockaday.

*In absence.

UNIVERSITY OF EDINBURGH

At a Graduation Ceremonial on July 18 the following degrees were conferred:

M.D.—E. D. Dalziel Dickson, [1]R. M. Ellison, [1]C. Hurwitz, [1]G. K. Mackenzie, R. Morrison, [1]F. H. Patel, [2]A. T. Wallace.

PH.D.—O. M. Attia, M.B., Ch.B., [1]K. D. Lahiri, M.B., B.S.

M.B., CH.B.—W. R. Allan, F. G. Anderson, J. H. Andrew, P. J. Attwood, D. A. Baird, A. R. O. Bakare, P. G. McC. Banister, Irene L. Barbour, G. P. T. Barclay, H. C. Barr, Margaret N. Barr, D. C. Begg, K. I. G. Benson, Rosalind M. Bentley, M. McC. Bett, A. S. Binnie, J. K. Binns, A. W. Black, I. Black, W. D. Black, I. A. C. Blue, Jeanie K. McM. Boyd, R. G. Brackenridge, K. Bragan, B. J. Brown, R. H. Brown, N. L. M. Browne, A. T. Bruce, A. M. Brunton, O. J. Burton, Katharine M. Cameron, D. P. Campbell, G. D. Campbell, Patricia E. Campbell, T. Campbell, W. R. Cattell, K. Chambler, D. B. Clark, F. R. Clark, [2]K. Clark, [2]Elinor M. Cleland, J. G. Collee, I. F. Craik, R. D. Cranston, K. H. McL. Crofts, J. I. Cromarty, A. P. Cross, G. S. Cruickshank, A. G. Donald, A. H. Duncan, L. J. P. Duncan, Margaret Duncan (née Courtier), R. Duncan, I. M. Duthie, D. B. Eaton, J. McK. Edington, W. M. Fee, M. D. FitzGerald, R. Flett, A. V. Foote, Isobel D. M. Forster, Evelyn M. Fortune, G. M. Fraser, H. R. Fraser, A. Fraser-Darling, W. B. F. Galloway, J. A. L. Goringe, Sheila M. Gough, Mary E. Grant, J. V. Groundes-Peace, D. Hardy, G. K. Hargreaves, J. R. A. Harvey, Kathleen F. Hastings, Isabella B. Heath, Elspeth J. B. Home, W. P. Honeyman, A A. Hooper, I. M. Ingram, Elizabeth M. Innes, G. C. Irvine, Margaret F. Jamieson, D. D. Johnstone, Colina C. Jones, H. I. Jones, Myra S. Kaye, A. J. Keay, L. S. Keppie, [2]D. N. S. Kerr, P. Kessly, J. K. S. Kirkcaldy, D. M. D. Lambert, Kathleen M. Lamont, A. P. N. Lee, F. E. H. Lightbody, G. Livingston, W. Lumsden, W. K. Lutterodt, Anne B. McArthur, E. J. McCabe, J. J. Maccabe, D. T. McClements, R. H. MacDonald, W. B. MacGregor, J. MacIntosh, D. McIntyre, W. H. R. McIntyre, A. C. MacLean, N. MacLean, Margaret G. Macnaughton, D. C. MacPhail, D. O. Maisels, D. Malone, J. S. Manson, Catherine H. McK. Mellen, R. M. Melville, C. W. Mercer, K. R. Middleton, Barbara I. Miller, J. W. Morley, Margaret B. Morton, W. Muirhead, Flora Murchison, Anne McG. Murdoch, Isobel J. Murray, J. M. Myles, R. S. Nagle, J. W. Nicholson, H. I. A. Nisbet, G. A. K. Ogilvie, Mary C. W. Paterson, B. C. Paton, G. G. Patterson, J. S. Patterson, P. D. Powell, G. M. Priestman, W. P. Prinsloo, Edith I. Proctor, M. S. Rathbone, A. W. Rattrie, G. P. M. Raymond, Margaret E. Riddoch, J. G. Rider, I. A. J. Ross-Smith, Alice L. Scott, R. W. Scott, E. D. Sever, D. A. Shaw, D. R. Sim, I. H. M. Smart, F. W. G. Snell, J. H. Stephens, Anne B. Sutherland, H. L. Symon, I. B. Tait, Mona A. Thompson, D. E. Tulloch, Florence V. P. Turpie, R. C. Tyldesley, A. E. Ward, H. S. K. Watson, K. Wemyss, D. A. Westwood, D. S. White, A. R. Williamson, J. M. MacD. Wilson, [2]K. Wood.

The following diplomas were awarded:

D.P.H.—D. M. Cathie, J. R. Cellars, Bertha Macfie, G. P. McLauchlan, Jessie K. M. Main, A. M. Nelson, Leah V. Rosenbloom, Margaret L. Westwater.

D.I.H.—B. Bhar, D. Murray, A. Sen.

D.T.M.&H.—R. F. Antonio, V. D. Bayliss, G. Currie, K. Damodaran, E. A. Esin, I. K. Hay, G. S. Kambourian, K. Mahadeva, S. S. Pavillard, J. B. Ross, G. P. Shrivastwa, J. F. Smith.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—I. B. D. Middlemass, T. Philp, W. J. Weston, A MacD. Wilson.

DIPLOMA IN PSYCHIATRY.—A. K. M. Macrae.

CERTIFICATE IN MEDICAL ILLUSTRATION.—Nora Campbell, M.B., Ch.B.

The following scholarships, bursaries, prizes, etc., in the Faculty of Medicine were awarded:

Cameron Prize in Practical Therapeutics, Professor Tadeus Reichstein (University of Basle) and Professor Edward Calvin Kendall (University of Minnesota), jointly, in recognition of their fundamental researches leading to the discovery of cortisone. *Ettles Scholarship and Leslie Medal, Mouat Scholarship in the Practice of Physic*, and *Lawson Gifford Prize in Obstetrics and Gynaecology*, D. N. S. Kerr. *Scottish Association for Medical Education of Women Prize, James Scott Scholarship in Obstetrics and Gynaecology, Dorothy Gilfillan Memorial Prize, Keith Memorial Prize in Systematic Surgery*, and *Royal Victoria Hospital Tuberculosis Trust Medal*, Elinor M. Cleland. *Buchanan Scholarship in Obstetrics and Gynaecology*, H. C. Barr. *Conan Doyle Prize*, G. D. Campbell. *Beaney Prize in Anatomy and Surgery*, K. Clark; *proxime accessit*, D. N. S. Kerr. *Annandale Medal in Clinical Surgery*, K. Clark and B. C. Paton (equal). *Murdoch Brown Medal in Clinical Medicine*, Colina C. Jones. *National Association for the Prevention of Tuberculosis Prize*, C. W. Mercer. *Pattison Prize in Clinical Surgery*, D. McIntyre. *Murchison Memorial Scholarship in Clinical Medicine*, Margaret E. Riddoch. *Goodsir Memorial Fellowship in Anatomy and Physiology*, K. Krnjevitch. *George Guthrie Research Fellowship in Child Health*, J. W. Farquhar. *Ethicon Research Fellowship*,

S. R. Mukherjee. *Paterson Travelling Scholarship in Surgery*, A. D. R. Batchelor. *Crichton Research Scholarships*, G. D. Forwell, H. D. Ritchie, and I. W. Winchester. *Wilkie Surgical Research Scholarship*, E. J. Delorme. *George William Falconer Macnaughton Bursary in Physiology*, G. H. Begbie. *Whiteside Bruce Bursary*, R. J. Wilson and D. C. Flenley (equal). *Senior John Aitken Carlyle Bursary in Anatomy and Physiology*, G. J. Mackenzie; *proxime accessit*, Margaret C. Holderness. *Junior John Aitken Carlyle Bursary in Anatomy and Biochemistry*, D. Dow; *proxime accessit*, F. M. McGurk. *Mackenzie Bursaries in Anatomy*, Elizabeth L. Handasyde, A. O. Langlands, G. R. Sutherland, and D. Dow and B. I. Tyson (equal). *Gunning Victoria Jubilee Prize in Botany*, Jean F. Malcolmson. *Gunning Victoria Jubilee Prize in Obstetrics*, P. R. Myerscough. *Cunningham Memorial Medal and Prize in Anatomy*, T. McI. Stevenson. *Anderson Henry Prize in Botany*, D. H. N. Spence. *Maclagan Prize in Forensic Medicine*, Pearl K. Malasky. *Robert Wilson Memorial Prize in Chemistry*, R. J. Wilson. *Vans Dunlop Prize in Physics and Chemistry*, R. J. Wilson and I. B. Macleod (equal). *Vans Dunlop Prize in Botany and Zoology*, I. M. MacIntyre. MacGillivray Prize in Zoology, R. Lampard. *Ian Oswald Prizes in Anatomy*, I. D. Heath, P. H. Jaques, and F. B. McCue.

[1]In absentia. [2]Highly commended for thesis. [3]With honours.

UNIVERSITY OF LONDON

The title of Professor Emeritus of Chemistry as applied to Hygiene in the University has been conferred on Professor M. E. Delafield on his retirement from the Chair of Chemistry as applied to Hygiene at the London School of Hygiene and Tropical Medicine which he has held since 1928.

The title of Professor Emeritus of Anatomy in the University has been conferred on Professor M. F. Lucas Keene, on her retirement from the Chair of Anatomy at the Royal Free Hospital School of Medicine which she has held since 1924.

The title of Professor Emeritus of Physiology in the University has been conferred on Professor A. V. Hill, C.H., F.R.S., Professor of Physiology and Head of the Biophysics Research Unit at University College since 1926, on his retirement from his Professorship.

The title of Professor Emeritus of Zoology and Comparative Anatomy in the University has been conferred on Professor D. M. S. Watson, F.R.S., on his retirement from the Jodrell Chair of Zoology and Comparative Anatomy at University College, which he has held since 1921.

Mr. J. C. McClure Browne has been appointed to the University Chair of Obstetrics and Gynaecology tenable at the Postgraduate Medical School of London and attached to the Institute of Obstetrics and Gynaecology, from October 1.

UNIVERSITY OF MANCHESTER

The following candidates have been approved at the examinations indicated:

M.D.—[1]J. Ball, G. R. Crawshaw, S. Falk, [1]J. Marshall, E. V. Mellor, [1]M. D. Milne, M. H. Oelbaum, M. Swerdlow, [1]F. R. Wilde, J. L. D. Williams, B. Wolman.

FINAL M.B., CH.B.—*Old Regulations:* T. V. A. Harry, H. Holgate. *New Regulations:* N Berlyne, Fay Beswick, G. Bills, Angela Blundell, L. R. Boulger, J. D. Bradshaw, J. L. Bramhall, R. H. L. Brown, G. Clarke, [2]Jean K. M. Clift, P. Cole, Joan B. Cooke, D. D. Davies, M. J. Derbyshire, L. J. Dolan, Eva O. Faulkner, R. J. Fothergill, D. Grime, J. K. Harris, R. Hewitt, W. A. Heyworth, J. T. Hughes, J. L. Jackson, W. A. Johnstone, J. T. Leeming, L. Lipworth, P. F. Lister, Kathleen E. B. Meller, B. Naylor, Heather M. Panton, J. V. Parry, M. Pemberton, Odile M. E. P. Plantevin, Christine S. M. Reynolds, M. L. Reynolds, D. S. Rosenberg, M. H. Sheard, D. W. Sim, D. M. Somerville, Joyce K. Starkie, S. Stead, M. D. Susman, [3]J. W. Valentine.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part I:* O. J. Slowik, Edith M. Thorp.

[1]With commendation. [2]Distinction in medicine.

UNIVERSITY OF BIRMINGHAM

The Dean of the Faculty of Medicine, Emeritus Professor W. H. Wynn, Professor J. M. Smellie, and Professor F. A. R. Stammers have been appointed representatives of the University on the Standing Joint Committee of the University, the United Birmingham Hospitals, and the Birmingham Regional Hospital Board, and Professor T. McKeown has been nominated to the Board in the place of the late Sir Leonard Parsons.

Dr. J. J. Elkes, Lecturer in Pharmacology, has been appointed Professor of Experimental Psychiatry, from October 1, and Dr. R. D. Parker Lecturer in Obstetrics and Gynaecology, from July 1.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

M.D.—E. T. Anderton, W. H. R. Cook, J. G. K. Dean, A. J. Robertson, G. Wynne-Griffith.

CH.M.—N. O. K. Gibbon, A. F. Murphy.

PH.D.—P. K. Duraiswami, M.S., M.Ch.Orth., F.R.C.S.

M.RAD.—P. Haslam, G. Jarrett, A. C. Kurowski.

FINAL M.B., CH.B.—T. D. M. Adams, A. B. Anderson, I. Berman, P. J. Boultbee, Dorothy F. M. Burnett, G. E. Burrows, Marie D. Carroll, H. D. Cheetham, Sheila M. Cochrane, T. J. Dailey, F. J. Deakin, Jeanette Diamond, Cynthia J. Discombe, D. A. P. Evans, B. J. Fairhurst, M. Goldman, J. H. Green, Beryl L. Greenwood, Hilary A. Hagan, B. G. Haggart, R. A. Hardman, J. C. Hinchliffe, T. L. Hobday, A. W. G. Housby, J. A. Howe, D. O. Hughes, P. Hughes, J. S. Jones, K. V. Jones, R. Larkin, M. M. J. Lavoipierre, W. E. Lewis, W. M. MacKean, C. McNamara, Heather G. Mathews, J. B. Newton, Alice N. O'Brien, J. V. Occleshaw, E. Patrick, I. M. Quest, Esther M. E. Ramsay, J. G. Rigby, J. B. Rogers, Patricia M. Russell, F. Seymour, L. Sheargold, H. Silver, R. Smyth, W. J. Stanley, J. G. K. Thomas, V. R. Tindall, L. Tragen, Megan Traini, A. Unsworth, E. I. Waldman, K. Walley, K. Warburton, R. Wharton, R. M. Whelan, R. H. Williams, T. D. Williams, R. G. B. Willis, M. C. Winter, Mary M. Yewdall. *Passed in separate subjects:* Pamela Elliot, Morilee Garside, K. C. Greenwood, Roma McDonald, Ellen G. Williams, and D. Winter (medicine and surgery); K. M. Fraser, J. J. D. MacPherson, and S. J. Rogers (surgery and obstetrics and gynaecology); F. R. Howell (medicine and obstetrics and gynaecology).

D.P.H.—B. Devlin, M. Doherty, G. Fairclough, Wilhelmina N. Gaye, W. A. Glynn, H. M. Thomas.

DIPLOMA IN RADIOLOGY.—*Radiodiagnosis, Part II:* J. H. E. Carmichael, A. G. McCarey, D. R. Wallace-Jones. *Radiotherapy, Part II:* F. M. Hall, O. N. Saxena.

UNIVERSITY OF LEEDS

On the occasion of the installation of the Princess Royal as Chancellor of the University on November 9 the honorary degree of LL.D. will be conferred on Dame Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists.

Dr. F. M. Parsons has been appointed Research Fellow in Urology for one year in the first instance, from July 1, and Dr. A. L. Taylor part-time Lecturer in Preventive Medicine and Public Health, from October 1.

Dr. C. Fraser Brockington has resigned from the post of part-time Lecturer in the Department of Preventive Medicine on his appointment to the Chair of Social and Preventive Medicine in the University of Manchester, and Dr. F. Ridehalgh from the post of part-time Lecturer in Tuberculosis on becoming physician-in-charge of the chest unit of the United Oxford Hospitals. Both resignations take effect from September 30.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on July 17, with Sir David K. Henderson in the chair, the following were elected Fellows: R. W. Riddell, C. Clayson.

The following were elected Members: W. I. Card, P. C. Gupta, G. P. Shrivastwa, P. J. G. O'Connor, N. A. Lamberty, C. W. Howden, Lillian G. Moore, B. M. Jacobson, B. Snell, R. S. McNeill, J. H. Bruce, A. Gillis, R. E. Church, A. C. Houston, I. H. Hume, M. E. Wahba, R. B. Khambatta, K. Sinclair, J. T. Wright, V. D. Parekh, W. H. Lloyd.

The Services

Major-General K. A. M. Tomory, C.B., O.B.E., K.H.P., R.A.M.C., has been appointed Colonel Commander, R.A.M.C., in succession to Lieutenant-General Sir W. P. MacArthur, K.C.B., D.S.O., O.B.E., R.A.M.C., retired, who has resigned the appointment.

Major-General J. M. Macfie, C.B., C.B.E., M.C., K.H.S., R.A.M.C., has been appointed Colonel Commandant, R.A.M.C., in succession to Major-General R. E. Barnsley, C.B., M.C., R.A.M.C., retired, whose tenure has expired.

Colonel William Graham, O.B.E., T.D., R.A.M.C., has been appointed Honorary Colonel of a Territorial Army Unit, in succession to Colonel R. I. Poston, T.D., R.A.M.C. (deceased).

Air Vice-Marshal W. E. Barnes, C.B.E., R.A.F., has been appointed Honorary Surgeon to the King, in succession to Air Vice-Marshal F. J. Murphy, C.B., C.B.E., R.A.F., who has vacated the appointment on retirement from the R.A.F.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending July 21 (No. 29).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending July 21 (*a*)	(*b*)	(*c*)	(*d*)	(*e*)	1950 Corresponding Week (*a*)	(*b*)	(*c*)	(*d*)	(*e*)	1942–50 England & Wales Corresponding Week Highest	Median	Lowest
Diphtheria	30	3	16	1	1	46	4	13	3	2	707	247	46
Deaths	—	—	—	—	—	1	—	—	—	—			
Dysentery	301	81	90	2		166	8	109	2	—	249	105	56
Deaths		—		—					—				
Encephalitis, acute	12	—		—		14	4	—	—		14	3	—
Deaths		—			—		1			—			
Erysipelas			17	5	6			21	—	4			
Food-poisoning	188	15		2		228	17		3				
Infective enteritis or diarrhoea under 2 years				13	37					23			
Deaths	10		3	1	—	20		2	4	1			
Measles*	6,306	155	174	177	155	8,754	601	197	75	229	8,754	5,502	2,401
Deaths		—	—	—	—		—	—	—	—			
Meningococcal infection	37	2	17	2		38	2	22	—	1	89	45	25
Deaths		—	—				—	1					
Ophthalmia neonatorum	47	2	13	—		37	2	13	—	1	110	66	37
Pneumonia, influenzal	292	11	—	1	4	293	17	5	3	—	481	374	293
Deaths (from influenza)†	3	—	—	—	—	6	1	1	—	—			
Pneumonia, primary			97					110					
Deaths	104	13		15	4	114	24		3	4			
Poliomyelitis, acute :													
Paralytic	61	5	15	2	1	260	28	58	18	5	260	17	5
Non-paralytic	73	2											
Deaths§	4	—			—	13	3			—			
Puerperal fever			10				—	6					
Puerperal pyrexia‖	89	9	8	—	1	94	7	9	2	—	154	133	94
Scarlet fever	830	80	113	16	27	1,153	67	98	50	53	2,107	1,254	936
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			133	38				170	44				
(2) Tuberculosis, non-respiratory			41	7				28	1				
(1) Deaths	135	19	20	7	10	133	17	19	4	9			
(2) Deaths		6	11	2	2		1	7	1	5			
Typhoid fever	5	—	—	2	3	6	—	1	—	1			
Deaths¶	—	—	—	—		—	—	—	—		62	22	11
Paratyphoid fever	37	4	3 (B)	—		5	—	—	—	7 (B)			
Whooping-cough	3,380	185	294	74	79	3,881	303	205	23	86	3,881	2,082	1,128
Deaths	3	—	—	—	—	2	—	—	1	—			
Deaths (0–1 year)	198	23	29	10	16	207	27	38	15	16	359	274	207
Deaths (excluding stillbirths)	3,968	630	538	119	153	4,092	611	550	108	146	4,187	3,926	3,621
Annual death rate (per 1,000 persons living)			11.0					11·0					
Live births	7,121	1,219	970	242	401	6,758	1,142	913	235	443	9,687	7,295	6,052
Annual rate per 1,000 persons living			19·9					18·3					
Stillbirths	160	27	26			181	29	22			241	207	152
Rate per 1,000 total births (including stillborn)			26					24					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Infectious Diseases

The largest changes in the number of notifications of infectious diseases during the week ended July 21 were an increase of 103 for whooping-cough, and decreases for measles 1,356, and acute pneumonia 56.

The largest declines in the incidence of measles were Devonshire 175, Lancashire 140, Kent 114, Carmarthenshire 107, Essex 105, while the largest exception to the general trend was an increase of 43 in Surrey. The largest fluctuations in the local returns of diphtheria were an increase of 3 in Lancashire, and a decrease of 4 in Yorkshire West Riding. Seven of the 30 cases of diphtheria were notified in Liverpool C.B. The only variations in the trends of whooping-cough of any size were increases in Essex 37, Yorkshire East Riding 45, Yorkshire West Riding 44, and a decrease of 46 in Warwickshire. Only small fluctuations occurred in the local returns of scarlet fever. The incidence of scarlet fever during the past month has been considerably below the level for the corresponding period of the three preceding years.

The notifications of paratyphoid fever were 8 more than in the preceding week. The largest returns during the week were: Lancashire 8; Sussex, Brighton C.B. 6; Kent 5.

The notifications of acute poliomyelitis were 14 more than in the preceding week. Decreases were recorded in the number of notifications in the three most important centres of the previous week—Warwickshire, Yorkshire West Riding, and Kent, where the falls were 16, 9, and 6, respectively. The largest returns during the week were Lancashire 15 (Liverpool C.B. 10, Manchester C.B. 3); Yorkshire West Riding, 12 (Rotherham R.D. 5); Warwickshire, 12 (Birmingham C.B. 5, Coventry C.B. 3); Kent, 11 (Orpington U.D. 9); Staffordshire, 7 (Stoke-on-Trent C.B. 3); London, 7.

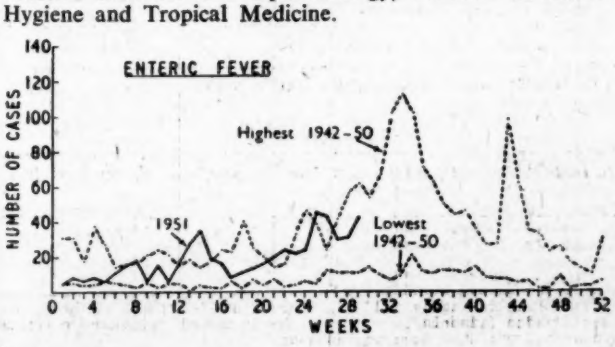
A rise of 9 occurred in the number of notifications of dysentery. The chief feature of the returns during the week was a rise of 22 in London. The largest returns were London, 81 (Islington 16, Chelsea 13, Lewisham 10; the other 42 cases were notified in 16 boroughs); Lancashire, 48 (Liverpool C.B. 16); Yorkshire West Riding, 24 (Saddleworth U.D. 11).

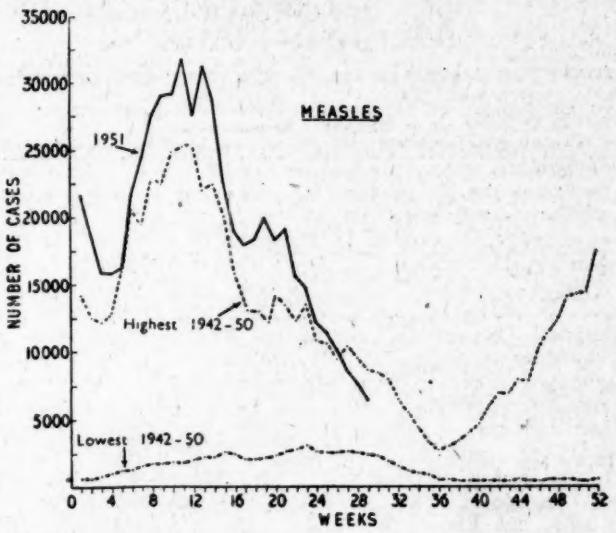
Poliomyelitis

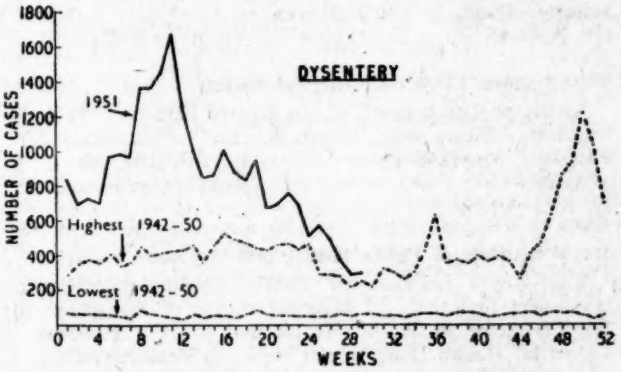
An abnormally large proportion of non-paralytic cases continues to be a feature of the disease. In the week ending July 28 these comprised 58% of total notifications, compared with 59% in the preceding week, and for this week there was a drop of 13 in the total notifications.

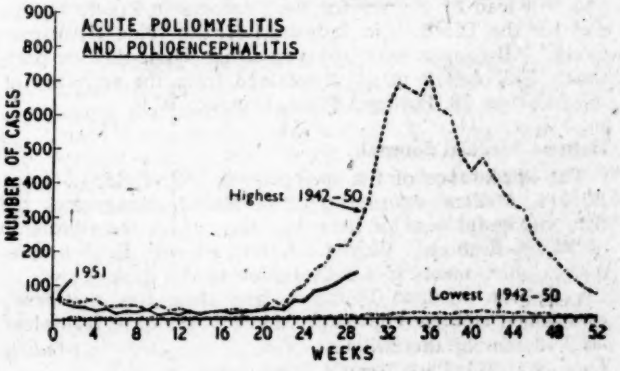
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - -, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending July 28

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 758, whooping-cough 3,261, diphtheria 36, measles 5,258, acute pneumonia 308, acute poliomyelitis 121, dysentery 226, paratyphoid fever 53, typhoid fever 8.

It is estimated that in England and Wales there are about 25,000 persons who were born deaf. In addition there are the hard of hearing, who are about ten times as numerous as the truly deaf. Up to date 140,000 hearing-aids have been supplied free of charge by the National Health Service, but there remain over 100,000 on the waiting-lists. Referring to these figures on July 6, the Minister of Health said that this was an entirely new service, and to have supplied in three years more than half of a need which was never met before was no mean achievement. Output had expanded considerably during the year, but it could not be expected to go much higher, for rearmament imposed a heavy new demand upon all sections of the electrical industry, especially for the production of batteries.

Medical News

Epsom College

The ninety-eighth annual general meeting of the governors of Epsom College was held in London on July 18. The results of the last election of pensioners and foundation scholars were announced by the chairman as follows: *Foundation Scholars*, J. D. Hardy, A. P. J. Henry, D. T. Jones, A. H. Lachlan, R. C. Lewis, C. S. Lillie, and D. G. D. Wight. *Pensioners*, Dr. J. Good, Mrs. V. B. Lillie, Mrs. E. M. Baynes, Dr. C. W. Ellison, and Dr. Edith K. P. Harris. The chairman emphasized that the increased fees which would come into force at Michaelmas, 1951, were wholly required to meet widespread rises in costs. The annual report of the council to the governors and the income and expenditure account for 1950 were approved. The following members of the council were re-elected for a further period of three years: Mr. Edward N. S. Adams, Mr. George H. Allen, Mr. James R. H. Turton, Mr. W. L. Cutler, Mr. Ronald W. Raven, Surgeon Vice-Admiral Sir Reginald Bond, Mr. J. R. Hovenden, Dr. Henry Robinson, Dr. Noel E. Waterfield, and Professor R. J. Willan.

West London Medico-Chirurgical Society

At the annual meeting of the society held on July 4 the following officers were elected for the forthcoming year: President, Mr. B. Sangster Simmonds; treasurer, Mr. G. B. Woodd-Walker; secretaries, Dr. Oswald Savage and Dr. G. R. Fearnley.

Royal Institute of Public Health and Hygiene

The Royal Institute of Public Health and Hygiene announces that the next biannual course of instruction for the Certificate in Public Health and for the Diploma in Industrial Health (Part I) will begin on Friday, October 5, and will lead to courses for the Diploma in Public Health and for the Diploma in Industrial Health (Part II) respectively. All courses may be taken either whole-time or part-time. Full details may be obtained from the secretary of the Institute, 28, Portland Place, London, W.1.

Hebrew Medical Journal

The appearance of the spring issue, Vol. 1, 1951, of the *Hebrew Medical Journal (Harofé Haivri)* inaugurates the 24th successful year of its publication under the editorship of Moses Einhorn. Written in Hebrew, with English summaries, the *Journal* is a contribution to the development of the Hebrew medical literature, and thus aids the newly established Hebrew University Medical School in Jerusalem. The address of the editorial office of the *Hebrew Medical Journal* is 983, Park Avenue, New York, 28, N.Y.

Medicine in Nigeria

The *West African Medical Journal*, which was suspended in 1938, is to resume quarterly publication in January, 1952, at an annual subscription of 1 guinea. It is published by the Secretariat at Ibadan.

Supplementary List of Approved Names of Drugs

The British Pharmacopoeia Commission has issued the following approved names of drugs: aloxidone (for 3-allyl-5-methyloxazolidine-2:4-dione, malidone); cyanocobalamin (vitamin B_{12}, anacobin, cobione, cytamen); di-iodohydroxyquinoline (8-hydroxy-5:7-di-iodoquinoline, diodoquin); domiphen bromide (dodecyldimethyl-2-phenoxyethyl-ammonium bromide, bradosol); ethyl biscoumacetate (ethyl 4:4′-dihydroxydicoumarinyl-3:3′-acetate, pelentan, tromexan); ethyl methimazolate (2-carbethoxythio-1-methyliminazole); methimazole (2-mercapto-1-methyliminazole, mercazole); methorphinan (3-hydroxy-N-methylmorphinan, dromoran is the hydrobromide); sulphafurazole (5-*p*-aminobenzenesulphonamido-3:4-dimethyl*iso*oxazole, gantrisin).

COMING EVENTS

Institute of Ophthalmology

Sir Cecil Wakeley, President of the Royal College of Surgeons of England, will deliver the inaugural lecture of the new academic year at the Institute of Ophthalmology, Judd Street, London, W.C., on Wednesday, October 3, at 4 p.m. The annual dinner of the Institute will be held at the Rembrandt Rooms, 10, Thurloe Place, South Kensington, S.W., at 7.30 for 8 p.m. the same evening. Tickets (18s. 6d. each) may be obtained from the secretary of the Institute.

Chemicals in Food

A conference organized by the Food, Agriculture, and Fine Chemicals Groups of the Society of Chemical Industry on problems arising from the use of chemicals in food will be held at the Wellcome Research Institution, 183–193, Euston Road, N.W.1, on September 27 and 28. Full details of the programme may be obtained from the assistant secretary, Society of Chemical Industry, 56, Victoria Street, London, S.W.1. The registration fee is 10s. for members of the society and £2 for non-members.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday

NATIONAL HOSPITAL, Queen Square, London, W.C.—August 15, 5.15 p.m., *"The Physical Aspects of Encephalography and Their Practical Applications."* cinematograph demonstration by Dr. Graeme Robertson (Melbourne, Australia).

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Registrar in Obstetrics and Gynaecology at Newmarket General Hospital*, E. Z. Milian, M.D., *Senior Surgical Registrar, East Suffolk and Ipswich Hospital*, E. M. Elmhirst, M.B., B.S., F.R.C.S.

ELLIS, JOHN ROGERS, M.B.E., M.B., M.R.C.P., Assistant Physician, The London Hospital, Whitechapel, E.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—*House-surgeon (Senior House Officer Grade)*, J. M. Jones, M.B., B.S., F.R.C.S. *(Corrected announcement.)*

MCCARTHY, DENIS, M.D., M.R.C.P.I., D.C.H., Lieutenant-Colonel, Indian Medical Service (retd.), Medical Officer to Geriatric Unit, St. Patrick's Home, Carrick-on-Shannon, Co. Leitrim, Ireland.

PICKUP, J. W., M.D., D.P.H., County Medical Officer, Worcestershire.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Drewitt.—On June 17, 1951, at "Fairview," Tattenhall, Cheshire, to Kathleen (formerly Blair), S.R.N., wife of Alfred H. Drewitt, M.R.C.S., L.R.C.P., a son—Paul Alfred Blair.

Mather.—On June 6, 1951, at York, to Maud (formerly Buchanan), wife of John S. Mather, M.B., Ch.B., a daughter.

DEATHS

Campbell.—On July 26, 1951, suddenly, at 30, Cambridge Park, Wanstead, London, E., Alister Campbell, M.B., Ch.B., D.O.M.S., aged 53.

Dixon.—On July 24, 1951, after an emergency operation, Robert Halstead Dixon, M.B., of 21, Mount View, Ealing, London, W., aged 75.

Drawbridge.—On July 21, 1951, at St. Leonards-on-Sea, Sussex, Wilfred Ralph Leycester Drawbridge, M.R.C.S., L.R.C.P.

Gellert.—On July 31, 1951, at West Hayes, South Petherton, Somerset, Harry Herbert Gellert, M.B., Ch.B.

Lloyd.—On July 27, 1951, at Milford, Surrey, John Ross Lloyd, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired.

Macleod.—On July 31, 1951, at the Royal Portsmouth Hospital, Malcolm Bonar Macleod, M.B., Ch.B., Surgeon Captain, R.N., retired, of 1, Clarendon Towers, Southsea, aged 59.

Meadows-Ryley.—On July 24, 1951, suddenly while on holiday, Charles Meadows-Ryley, M.B., B.Ch., of 40, Bromley Road, Beckenham, Kent, and 56, Wimpole Street, London, W., aged 65.

Paul.—On July 22, 1951, at 8, Park Terrace, The Park, Nottingham, Edmund William Paul, M.R.C.S., L.S.A., aged 89.

Sacki.—On July 31, 1951, at Eastern General Hospital, Edinburgh, Fritz Ludwig Sacki, M.D., of the Church of Scotland Hospital, Tiberias, Israel, aged 58.

Simmons.—On July 27, 1951, George Alan Simmons, M.R.C.S., L.R.C.P., of Tydehams, Newbury, Berks.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Cleaning the Empties

Q.—*I am a dispensing country doctor and would like to know what is the best way of cleaning "returned empty" medicine bottles. The method must be appropriate for small-scale use.*

A.—Many bottles need no other treatment than thorough rinsing with a strong jet of water, preferably warm water. This is best carried out by means of a bottle-washing jet, which consists of a fine metal jet attached to a base and through which a strong stream of water may be forced merely by pressing the bottle down on to the base, the metal jet projecting into the bottle. Such jets are relatively cheap.

Dirtier, and particularly greasy, bottles can easily be cleansed by soaking for a short while in a solution of liquor sulphestolis *B.P.C.* (1 oz. to a gallon—6.3 ml. to 1 litre—of hot water). After rinsing, the bottles should be very clean and bright. If necessary, a satisfactory routine for all bottles could be soaking in this solution followed by a thorough rinsing with a jet of the type indicated above. Very dirty bottles or those to which substances cling obstinately may be treated for a few moments with a bottle brush and a few drops of neat sulphestol, followed by a thorough rinse. A few bottles may need a quick rinse with dilute hydrochloric acid, followed by thorough rinsing.

Respirators for Children with Poliomyelitis

Q.—*What is the most suitable type of artificial respirator for children suffering from poliomyelitis? It is desired to use the respirator in a hospital in India.*

A.—There is still no breathing machine which will satisfactorily displace the cabinet or tank ("iron lung") for general use. The standard adult-size machine will accommodate very small children quite satisfactorily, although there are machines on the American market constructed for infants and children up to 3 years of age.

The speeds of all respirators should be finely variable with a range of between 14 and 30 respirations per minute. Cuirass or jacket types ("chest respirators") are also available commercially, but they have a more limited use and lower efficiency. There are two firms in this country producing cabinet respirators, both types being good examples of their kind. There are several manufacturers in the U.S.A. and at least one Dutch. Changes incorporated in recent British prototypes, while not altering the basic design of cabinet types, embody improvements adopted from experience with earlier types. The problem of efficient respirator design is now being studied by a Ministry of Health Working Party.

Fishy Water

Q.—*Is a "fishy," chlorinous taste and smell in purified town water always due to excess of chlorine? The water is originally pumped from a running river.*

A.—Tastes in water are divided for convenience into a number of categories, of which "fishy" and "chlorinous" are two.

As the water supply in question is derived from a river, it may be assumed that fish are contained in it, and it is common experience that dead fish, if present in considerable numbers, do at times impart a characteristic taste to water, disappearance of the taste coinciding with the removal of the fish. On the other hand, fishy tastes may result from the presence of sufficient concentrations of microscopic organisms. Certain diatoms, such as *Asterionella* and *Tabellaria*, some of the Chlorophyceae, particularly *Eudorina*, *Pandorina*, and *Volvox*, and some of the Protozoa, such as *Ceratium*, *Synura*, and *Uroglena*, can render water quite unpleasant by reason of the fishy taste to which they give rise.

A chlorinous taste may be caused by chlorine itself or by a combination of chlorine with various impurities in the water. There are some who contend that "free" chlorine—and in this instance free chlorine may be considered as that remaining after all chlorine deviants have been oxidized—imparts no taste in the concentrations experienced in water supply practice. The water under consideration is, however, from a river which doubtless contains organic matter, and it is probable that the chlorinous taste is derived from combination of the chlorine with this matter. Without a knowledge of the full circumstances surrounding the particular water supply it is not possible to give a considered opinion, but it is possible that the taste would be removed by increasing the dose of chlorine to a point where the potentially taste-producing contaminants in the water are oxidized by the chlorine instead of combining with it.

Analgesia for Episiotomy

Q.—*When in a primipara the head is distending the perineum but unable further to advance because of the tightness of the orifice, it is understood that the accepted teaching is that the patient should be anaesthetized and an episiotomy carried out. I wish to know whether, in order to avoid a general anaesthetic, a local analgesic—e.g., 2% procaine—could be rapidly injected around the site for the episiotomy and an incision made without any general anaesthetic. Alternatively, if a general anaesthetic must be administered, would sodium thiopentone injected intravenously be considered suitable?*

A.—Local analgesia of the kind suggested is the ideal in these circumstances. All that is necessary is to infiltrate along the proposed line of incision, protecting the foetal head with a finger in the vagina. If the injection is made to extend well to the side of the incision and to include the vaginal wall it will also suffice for the subsequent repair. If the resistant perineum starts to tear and there is no time to prepare and inject procaine, a few drops of chloroform on a mask gives sufficient analgesia for rapid episiotomy. In that case local infiltration with procaine is carried out later for the purpose of the repair.

Sodium thiopentone can be used, but has the disadvantage that with loss of consciousness the patient may fail to complete the delivery herself. Moreover, by itself it is generally inadequate for accurate suturing. It might be expected to cause asphyxia neonatorum, but in practice this is rarely the case.

Battle Shock

Q.—*What is the rationale of insulin therapy in cases of battle shock? Is this condition now regarded as being a schizoid-depressive reaction rather than a psychoneurosis? Is insulin therapy preferable to electro-convulsion therapy and/or continuous narcosis?*

A.—The insulin treatment which is given for battle shock is not the same as the insulin treatment which is given for schizophrenia. The latter requires the administration of sufficient insulin in the fasting state to bring about hypoglycaemic coma, the former only a sufficient dose to produce a soporose state from which the patient can easily be roused. There are therefore very slight risks in the "modified" treatment. After being roused from insulin sopor the battle casualty will usually take an enormous breakfast with great appetite. In the course of weeks he will put on weigh:

rapidly and so recover from the previous physical exhaustion which would have been an important indication for the treatment. Battle shock may take many symptomatic forms, but anxiety and hysterical and neurasthenic symptoms are usually prominent. The condition is not regarded as a schizoid-depressive reaction but simply as a reaction—anxious, hysterical, or depressive according to the outstanding symptoms. There is no harm in calling it psychoneurotic as long as it is remembered that it may be shown under grave physical and emotional stress by any individual, however stable, and does not necessarily require a neurotic predisposition. Electro-convulsive therapy is rarely used in these states, and only if special indications exist. Continued narcosis is used both commonly and very successfully, and can perfectly well be combined with modified insulin treatment, most usually by giving the latter to ensure steady convalescence after an original severe anxiety state has been soothed by sleep treatment.

Deck Legs

Q.—*What is the aetiology and treatment of "deck legs" or "tropical legs"? I mean the oedema of the legs frequently found in passengers in ships in tropical zones. This oedema is often very tense, usually involves both legs and spreads up to the knees, so that the victim sometimes finds it impossible to put on her shoes on arrival at her destination. All my own cases have occurred in women passengers, never in a member of the crew. Physical examination shows no other abnormality—no albumin in the urine and no increase in the blood pressure. My colleagues have suggested various explanations such as allergy, photosensitivity, continued bending of knees over a deck chair, all of which I think I can exclude in my cases. Another suggestion is that the condition is due to absorption of salt-saturated air of high humidity through the skin. However, I should have thought that this would be counteracted by the loss of salt in profuse sweating. Also, placing the patient on a salt-free diet does not in my experience control the condition.*

A.—The questioner seems to have excluded all the more common causes of oedema in these cases, although one wonders if he can always exclude the mechanical effect of the deck-chair. Other possibilities to be considered are:

(1) *Effect of Sunburn:* Blum (1945) quoted Menkin's work in which he showed that ultra-violet irradiation acts on the cells of the Malpighian layer to produce a dilator substance, leucotaxin. Leucotaxin increases capillary permeability and thus causes oedema.

(2) *Posture Without Mechanical Obstruction:* in the Tropics the usual increase in skin circulation seen with exposure to heat, especially radiant heat, will take place. If the blood flow to the skin of the lower limb increases and the capillary pressure rises at the same time as the individual becomes less active because of the heat, there is danger of pooling and so of postural oedema. This would fit in with the observation that active persons (crew) are not affected.

(3) *Endocrine Activity:* swelling of the hands and feet is a common complaint of many people in the heat; it has never been really satisfactorily explained (Best and Taylor, 1945). Apparently similar rapid swelling under artificial heat conditions may be produced by the administration of deoxycortone, and Ladell (1949) occasionally observed it in subjects sweating freely, drinking copiously, but not taking any salt. He advanced the theory that this rapid accumulation of extracellular fluid in the heat was due to a slowing up of the transfer of fluid from the extra- to the intra-cellular compartments, which could be mediated by parenterally administered hormone and sometimes by increased activity of the adrenal cortex. The sequence of events would then be, briefly: (1) heat stress; (2) increased activity of adrenal cortex; and (3) retention of fluid in extra-cellular compartments. Restriction of salt, especially in a patient already losing salt in her sweat, would increase the stress and further increase the activity of the adrenal (Conn, 1944), thus worsening the patient's condition. In any case the clinical advisability of restricting the salt intake in an individual who is sweating freely is doubtful, in view of the danger of precipitating salt-deficiency heat exhaustion.

In the writer's experience "deck legs," however caused, is a self-limiting condition; it rarely lasts longer than a week or ten days. Protection against sunburn is advisable, resting with the feet up helps, and patients should be encouraged to take light exercise at other times and to drink plenty of water and take salt freely.

REFERENCES

Best, C. H., and Taylor, N. B. (1945). *Physiological Basis of Medical Practice*, p. 29. Baillière, Tindall and Cox, London.
Blum, H. F. (1945). *Physiol. Rev.*, **25**, 483.
Conn, J. W., and Johnston, M. W. (1944). *J. clin. Invest.*, **23**, 933.
Ladell, W. S. S. (1949). *Lancet*, **2**, 836.

Impairment of Memory

Q.—*Impairment of memory both of recent and remote events seems to be a very common symptom in many diseases of the brain, such as neurosyphilis and senile and pre-senile dementia. Could you please explain the mechanism by which such impairment is brought about? Is there any treatment for improving memory in the case of a young, non-syphilitic patient?*

A.—Impairment of memory is invariably found when there is any widespread lesion of the brain, or even any general interference with its function. Thus there are temporary impairments of memory in toxic, post-infective, and delirious states. It need not, perhaps, surprise us that this should be so, since memory is a function of the intact nervous system and like other functions, such as sensation and perception, muscular co-ordination, judgment and reasoning, suffers with any loss of any kind of that integrity. To answer the question by what mechanism does an impairment of cerebral structure bring about impairment of memory one would need to be able to answer the more fundamental question by what mechanism does the intact brain preserve memories—and on this point we have no precise information but only speculation.

There is no doubt that memory can be improved by training, and there are many training systems. But there are also wide differences between individuals in their power of recall which cannot be equalized out of existence by any training method. It is said, for instance, that Macaulay could repeat verbatim an entire page of *The Times* after a single reading. Furthermore, every individual is better at remembering some things—e.g., telephone numbers—than others—e.g., names. As a function, memory is probably not simple but complex.

Sugar and Spice and All that's Nice

Q.—*What does molasses consist of? Apart from its sugar content, has molasses any particular value in human nutrition?*

A.—Molasses is derived from the mother liquor from which cane sugar is crystallized. It contains 47% of cane sugar, 20.4% of dextrose and laevulose, 2.7% of extractives and colouring matter, 2.6% of minerals, and 27.3% of water. In black treacle the extractives and minerals are retained, laevulose and dextrose are increased at the expense of cane sugar, and water is slightly reduced. In golden syrup, the next stage of purification, dextrose and laevulose are again increased, water reduced, and the extractives and minerals about halved. Molasses is rich in most of the B vitamins and also in iron.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.
ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*
MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*
B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.